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STUDIES IN THE CHEMISTRY OF
SULPHUR AND OXYGEN HETEROCYCLES

A Thesis presented in part fulfilment
of the requirement for the Degree of
Doctor of Philosophy

by

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September 1989

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ACKNOWLEDGEMENTS.

Firstly, I thank my supervisor, Professor G.W. Kirby, for his help and guidance during the past three years. I would also like to thank the technical staff at the Department of Chemistry, Glasgow University, especially Mr. J. Gall for his advice on the running of n.m.r. spectra and Mrs. P. Tait and her colleagues for mycological assistance. I thank the inhabitants of the Loudon lab., past and present, and all others who took an interest in my work.

I thank also, Professor R.B. Cain, Department of Agriculture and Environmental Science, University of Newcastle-upon-Tyne, for his interest and for a sample of 4-n-butyrylpyrocatechol.

The financial support of the S.E.R.C. is also gratefully acknowledged.

Finally, I thank my parents for their continued support and interest, especially my mother for her excellent typing.

'The great tragedy of Science is the slaying of a
beautiful hypothesis by an ugly fact.'

Thomas H. Huxley, 'Biogenesis and Abiogenesis'.

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SUMMARY.

Chapter one deals with the generation and trapping of the S-oxides (sulphines) of thioaldehydes. A number of sulphines were generated at moderate temperatures (60°C - 80°C) by thermal retro-Diels-Alder reaction of sulfoxides, prepared by oxidation of thioaldehyde cycloadducts formed from various cyclic conjugates dienes. Adducts of the thioaldehydes thioxoacetophenone, 4-bromothioxoacetophenone, 4-nitrothiobenzaldehyde and thioxoacetonitrile with cyclopentadiene were prepared. The exo-thioaldehyde adducts with thioxoacetophenone and 4-bromothioxoacetophenone were oxidised to give cis sulfoxides. Trans sulfoxides were formed by oxidation of the endo-thioaldehyde adducts. Likewise, adducts of the thioaldehydes 1-propanethial, 4-bromothioxoacetophenone, thiobenzaldehyde and 4-nitrothiobenzaldehyde with anthracene were prepared. Oxidation of the 1-propanethial anthracene adduct gave a mixture of cis and trans sulfoxides. All other anthracene adducts were oxidised to give only the trans sulfoxides. An adduct of 4-nitrothiobenzaldehyde with thebaine was also prepared and oxidised to give its trans sulfoxide.

All trans sulfoxide adducts when heated in the presence of 2,3-dimethylbuta-1,3-diene, reacted to give the corresponding dimethylbutadiene cycloadducts with

complete retention of stereochemistry. The stereochemistry of all the sulphoxide adducts was determined by ^1H n.m.r. spectroscopy and various other chemical studies.

Chapter two deals with biosynthetic transformations involving muconolactones. Methods for the synthesis of 4-ethyl- and 4-n-propylpyrocatechol were devised. These were then fed to cultures of Pseudomonas putida. 4-Ethylpyrocatechol was metabolised to give 4-ethyl-muconolactone along with small amounts of 3-ethyl-muconolactone. 4-n-propylpyrocatechol, however, was recovered largely unchanged. 3-Ethylmuconolactone and the related ethyldilactone were prepared as possible substrates for the lactone isomerase enzyme of Rhodococcus ruber.

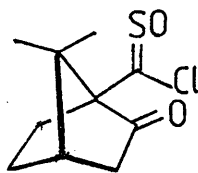
CHAPTER 1

The Generation and Trapping of the S-Oxides (Sulphines) of Thioaldehydes.

1. A Review of the synthesis and cycloaddition reactions of sulphines.

Introduction.

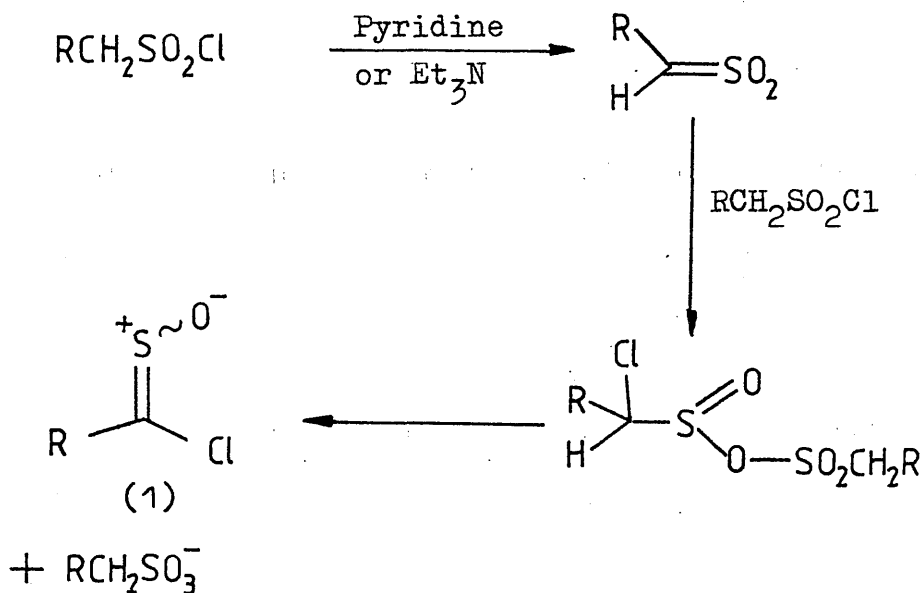
In recent years, there have been a number of reviews¹⁻⁷ on the chemistry of heterocumulenes of the type >C=S=O , which are known as sulphines. This name was proposed by Sheppard and Dieckmann⁸, in 1964, to indicate the structural relationship with species of the type >C=SO_2 which are known as sulphenes⁹⁻¹¹.



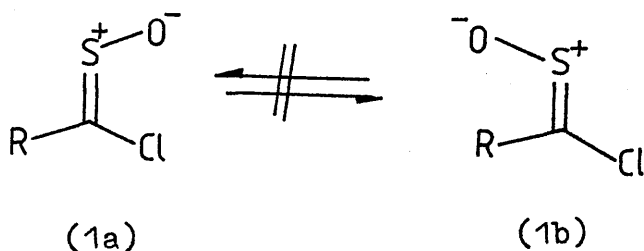
(1)

The first sulphine (1), a thioacyl chloride S-oxide was prepared by chance when Wedekind et al.¹² treated camphor-10-sulphonyl chloride with pyridine or triethylamine. The suggested sulphine structure however was not confirmed until about forty years later by King and Durst¹³ using spectroscopic methods.

In the early 1960's the reaction mechanism (Scheme 1) was clarified¹⁴ when it was shown that the formation of chlorosulphines could proceed via the intermediacy of a sulphene and a sulphinic-sulphonic anhydride. It was also shown¹⁵ that the cis (Z) (1a) and trans (E) (1b) geometric isomers of this sulphine were capable of existing independently, thus implying that the CSO grouping is bent (similar to SO₂) with a significant barrier to interconversion.



Scheme 1.

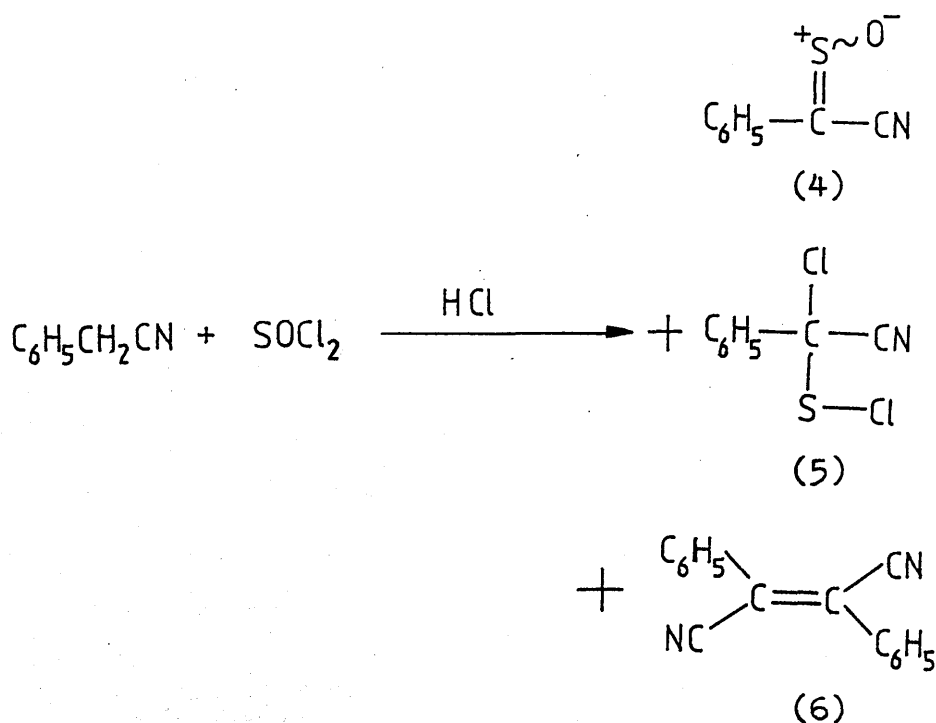


Following the scattered publications of the early sixties, sulphine chemistry began to develop rapidly and within the next few years, a large variety of substituted sulphines became known.

Stability of sulphines.

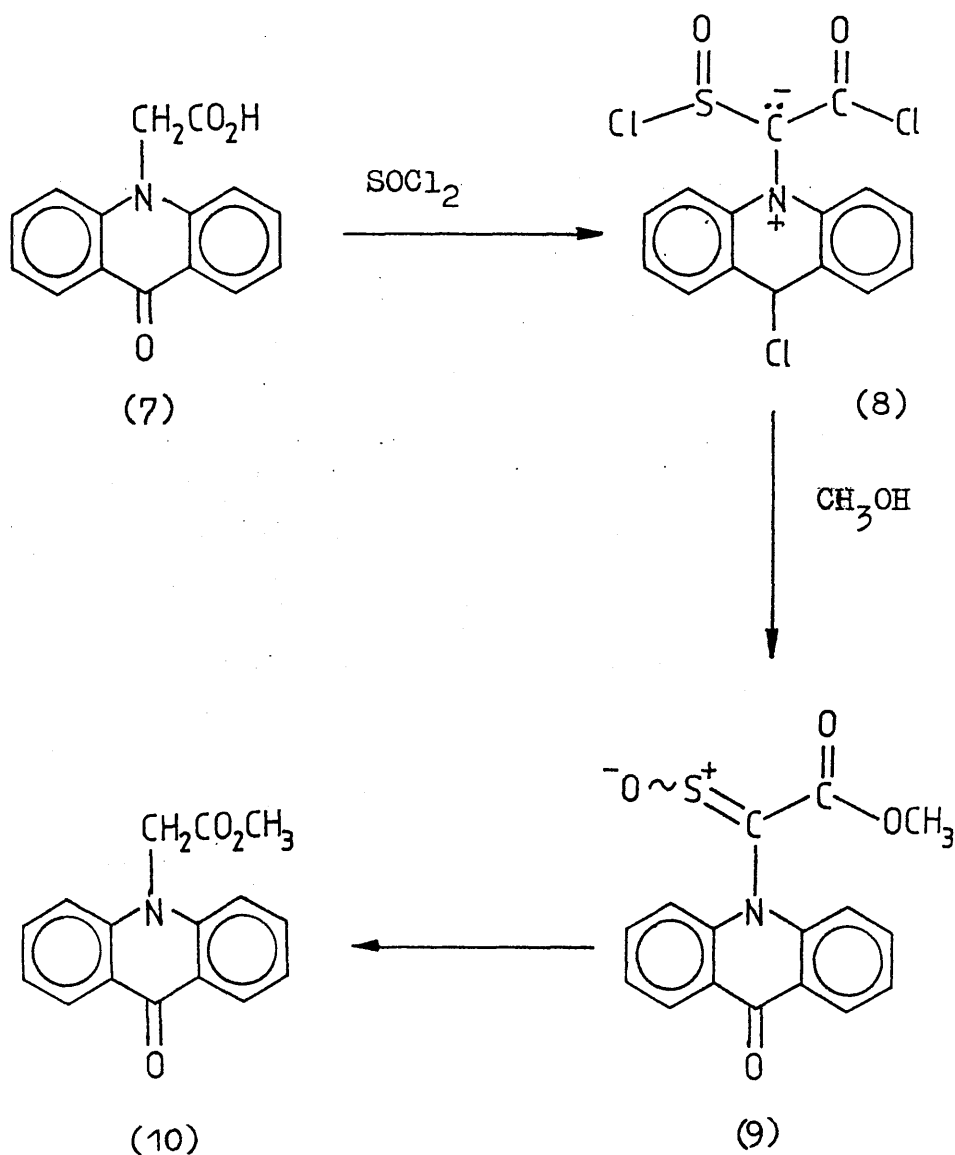
Generally speaking, sulphines are more stable than the corresponding thioaldehydes or thioketones and follow similar trends in their reactivity. Thus like thioketones and thioamides, thioketone and thioamide S-oxides are generally also stable and well studied species. In contrast, sulphines of thioaldehydes, like the parent species, tend to be reactive, transient intermediates. However, whereas thiobenzaldehyde has been reported to polymerise above -160°C ¹⁶, cis-thiobenzaldehyde S-oxide was found to be stable in the refrigerator at -20°C .¹⁷ Simple alkyl and aryl thioaldehyde S-oxides have been well characterised. For example, Bonini et al.¹⁷ having prepared cis-thiobenzaldehyde S-oxide were able unambiguously to determine the cis stereochemistry by n.m.r. spectroscopy. Likewise, thiopropanal S-oxide, the lachrymatory factor in onions (Allium cepa) was characterised firstly by Wilkens¹⁸ using infrared spectral data and then later by Virtanan et al.¹⁹ on mass spectroscopic grounds. Later still, Brodnitz and Pascale²⁰ unequivocally proved that the lachrymatory fraction of onions had the sulphine structure by its synthesis from propanesulphinyl chloride.

More reactive sulphines, having electron withdrawing substituents at the α carbon have also been prepared by this method. For example, Ohoka et al.²² were able to generate small amounts of phenylcyanosulphine (4) by the reaction of phenylacetone nitrile with an excess of thionyl chloride in the presence of a small amount of hydrogen chloride, at 0°C for 3 days (Scheme 3). They also observed as by-products α -chloro- α -cyanophenylmethanesulphenyl chloride (5) and trans- α,β -dicyanostilbene (6); they showed the latter to be a product of the thermal decomposition of the unstable sulphine (4).



Scheme 3.

Ning et al.²³ observed formation of a methoxycarbonyl sulphine in the course of derivatisation of 9-oxo-10-acridanacetic acid (7), a potential antiviral agent. When (7) was treated with thionyl chloride, the unusual intermediate (8) was isolated as crimson-red prisms. When this was further treated with methanol, the unstable sulphine, methyl 9-oxo- α -sulphinyl-10-acridanacetate (9) was generated which was readily cleaved by mild hydrolysis to give the ester (10) (Scheme 4).



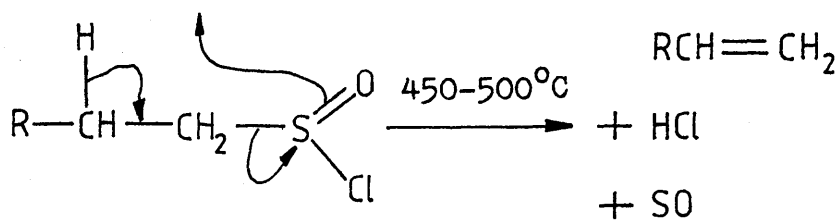
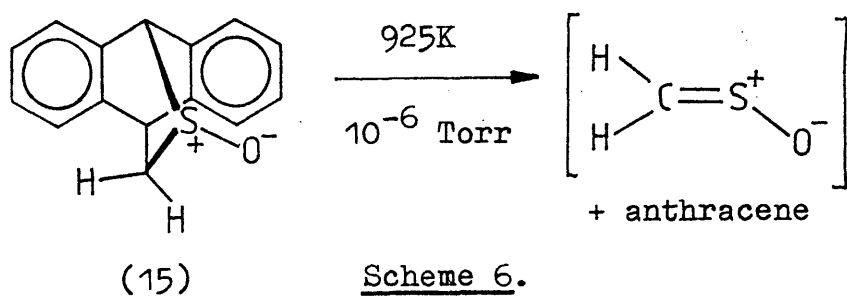
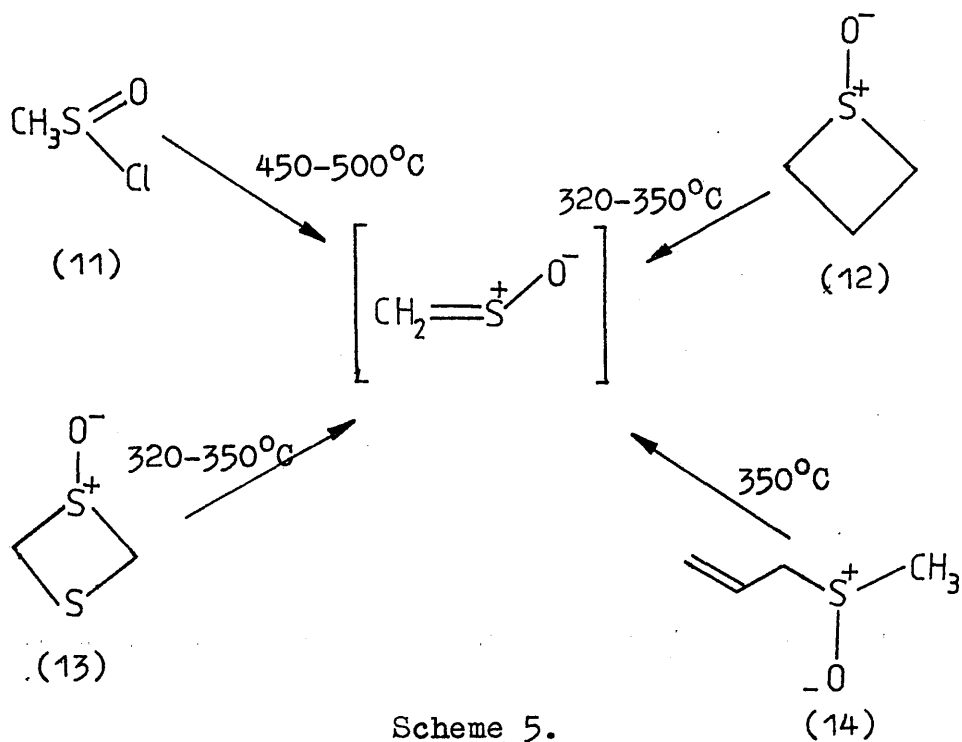
Scheme 4.

(ii) Thermolysis of sulphinyl compounds.

Although the simplest member of the sulphene class, $\text{CH}_2=\text{SO}_2$, can be generated from methanesulphonyl chloride by treatment with triethylamine^{1,11}, the corresponding sulphine cannot be obtained by similar treatment of methanesulphinyl chloride^{1,8,24}. Here, elimination of hydrogen chloride requires use of the flash vacuum pyrolysis (f.v.p.) technique^{25,26}. Block found that methanesulphinyl chloride (11), thietane S-oxide (12) and 1,3-dithietane-1-oxide (13) all served as precursors. Upon thermolysis they generated the parent sulphine, which was detected in the absorption cell of a microwave spectrometer attached to the pyrolysis system. The parent sulphine was also produced by thermal (f.v.p.) retro-ene reaction of allyl methyl sulfoxide (14) and trapped in an argon matrix at 18°K, thus allowing its study by infrared spectroscopy (Scheme 5). As expected, this sulphine was found to be an extremely reactive species with an estimated lifetime of about 30 mins. in the gas phase at ambient temperature²⁵.

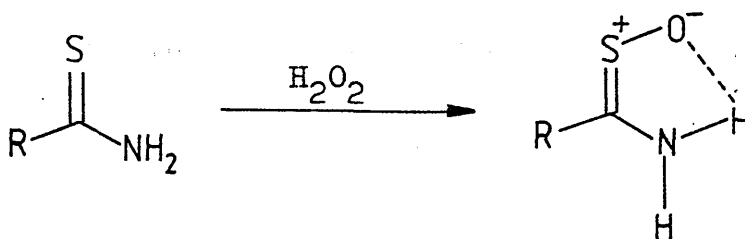
Recently Valee et al.²⁷ likewise generated methanethial S-oxide by thermal retro-Diels-Alder reaction (f.v.p.) of the anthracene adduct (15), (Scheme 6), and were able to establish the identity of the sulphine by n.m.r. spectroscopy at 173°K. Pyrolysis of ethane- and 2-propane-sulphinyl chlorides²⁵ however did not lead to production of sulphines. Instead, hydrogen

chloride, sulphur monoxide and ethene or propene respectively were produced via a Cope elimination (Scheme 7).



(iii) Oxidation of thiocarbonyl compounds.

This method is by far the most versatile one for the preparation of sulphines of stable thiocarbonyl compounds. A number of different oxidants have been used to prepare a wide range of sulphines. For example Walter and Curts²⁸ used hydrogen peroxide in methanol to oxidise a variety of primary thioamides to amino sulphines, which were stabilised by hydrogen bonding between the amino group and the sulphine oxygen atom (Scheme 8).

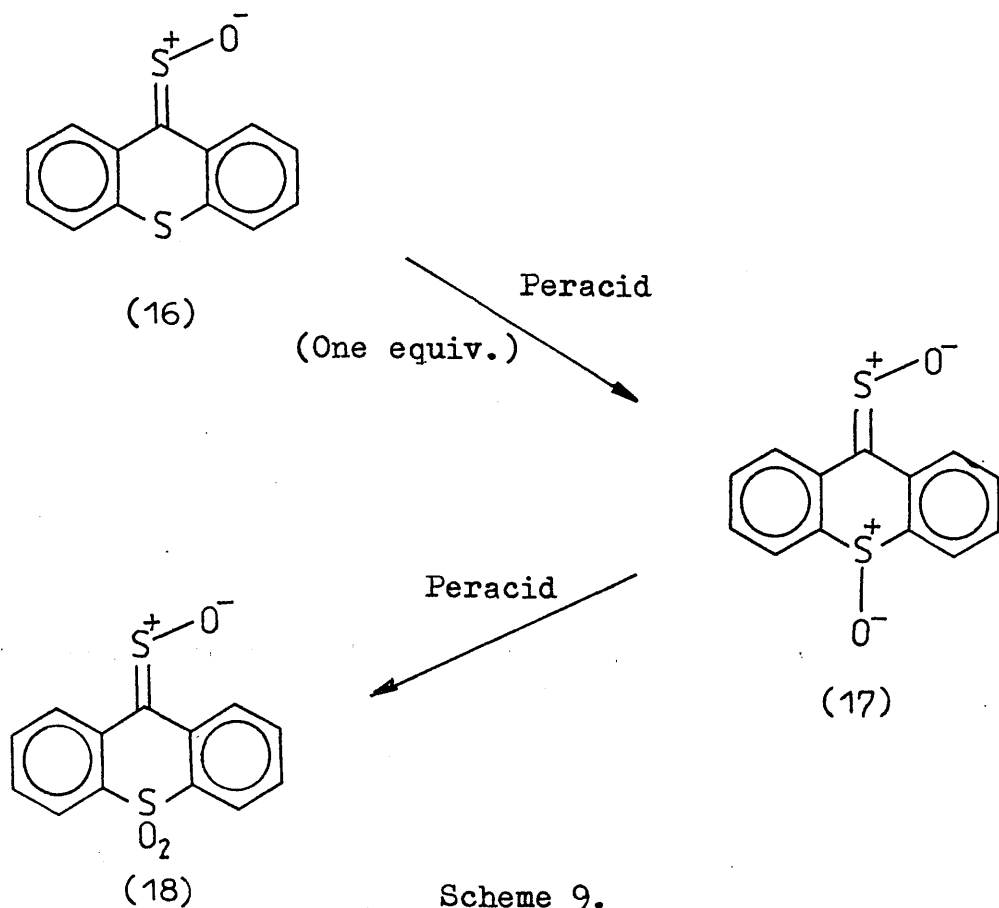


R = H, CH₃, CN, CH₂OCH₃, CH₂Ph, Ph.

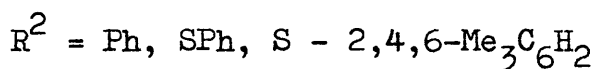
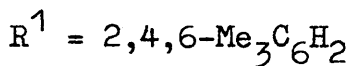
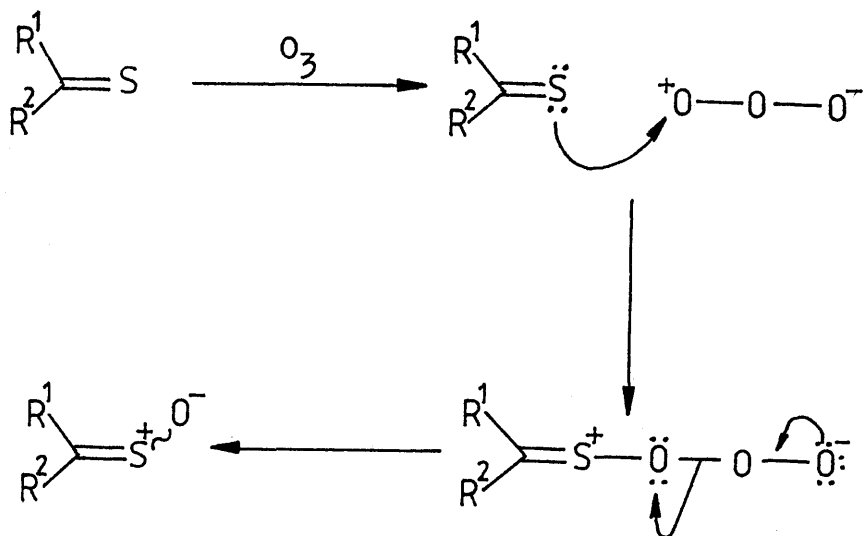
Scheme 8.

For oxidation of thioketones, controlled reaction was required to prevent overoxidation to ketones. Many thioketone S-oxides have been obtained using organic peracids. Zwanenburg²⁹ found that the sulphine (16) was produced with one equivalent of peracid. It was necessary to use only one equivalent of peracid as an

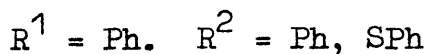
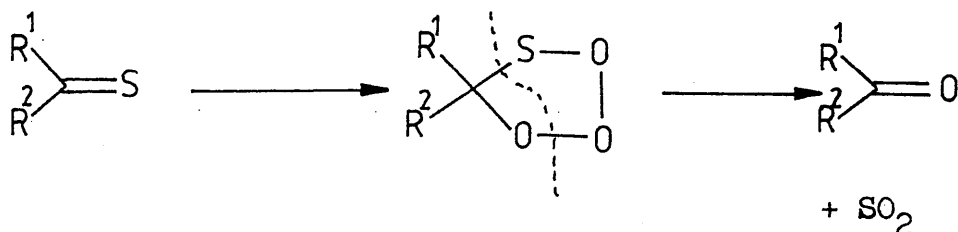
excess of oxident led to generation of the sulphoxide (17) and the sulphone (18) (Scheme 9).



Sulphines were obtained from sterically hindered thiocarbonyl compounds by treatment with ozone³⁰ (Scheme 10). In contrast, with unhindered substrates, treatment with ozone gave the corresponding carbonyl compounds which, it is thought³⁰, are formed as a result of cycloaddition with ozone followed by loss of sulphur dioxide. The latter process may be analogous to the cleavage of molozonides proposed by Criegee^{30a} (Scheme 11).



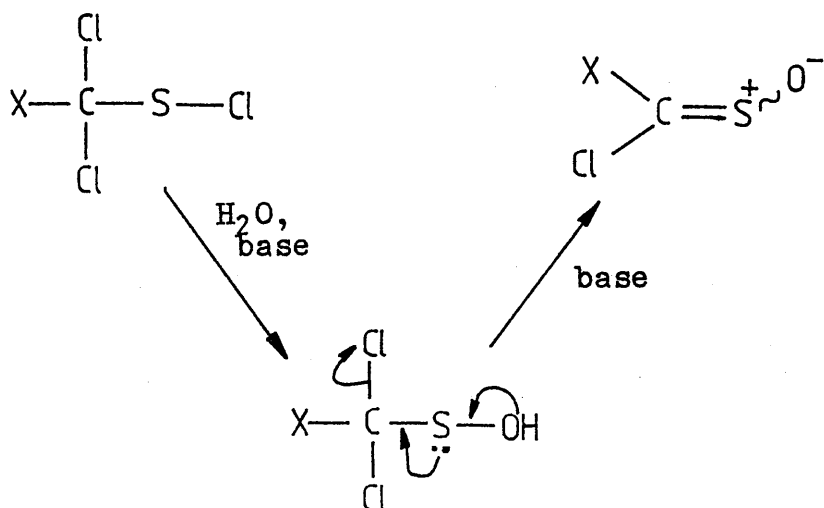
Scheme 10.



Scheme 11.

(iv) 1,3-Dehydrochlorination of chlorosulphenic acids.

Phillips and Ratts³¹ showed that hydrolysis of trichloromethanesulphenyl chloride in the presence of base gave the sulphenic acid which, after elimination of hydrogen chloride, gave the corresponding sulphine (Scheme 12).

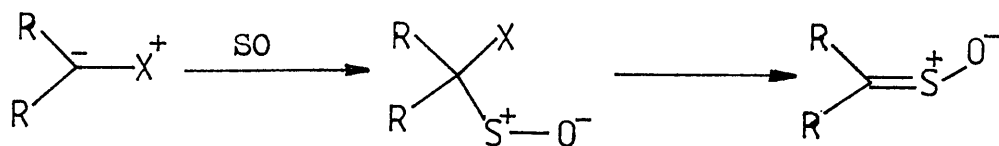


$\text{X} = \text{Cl}, \text{Ar}, \text{ArNHCO}.$

Scheme 12.

(v) Reactions of sulphur monoxide with diazoalkanes and ylids.

Bonini et al.³² prepared diphenylsulphine by reaction of diphenyldiazomethane with sulphur monoxide generated in situ by mild thermal decomposition of trans-2,3-diphenylthiirane S-oxide. They showed also³³ that phosphonium, sulphonium and pyridinium ylids react in a similar manner to give sulphines (Scheme 13).



$\text{X} = \text{N}_2$ $\text{R} = \text{Ph}$

Ph_3P

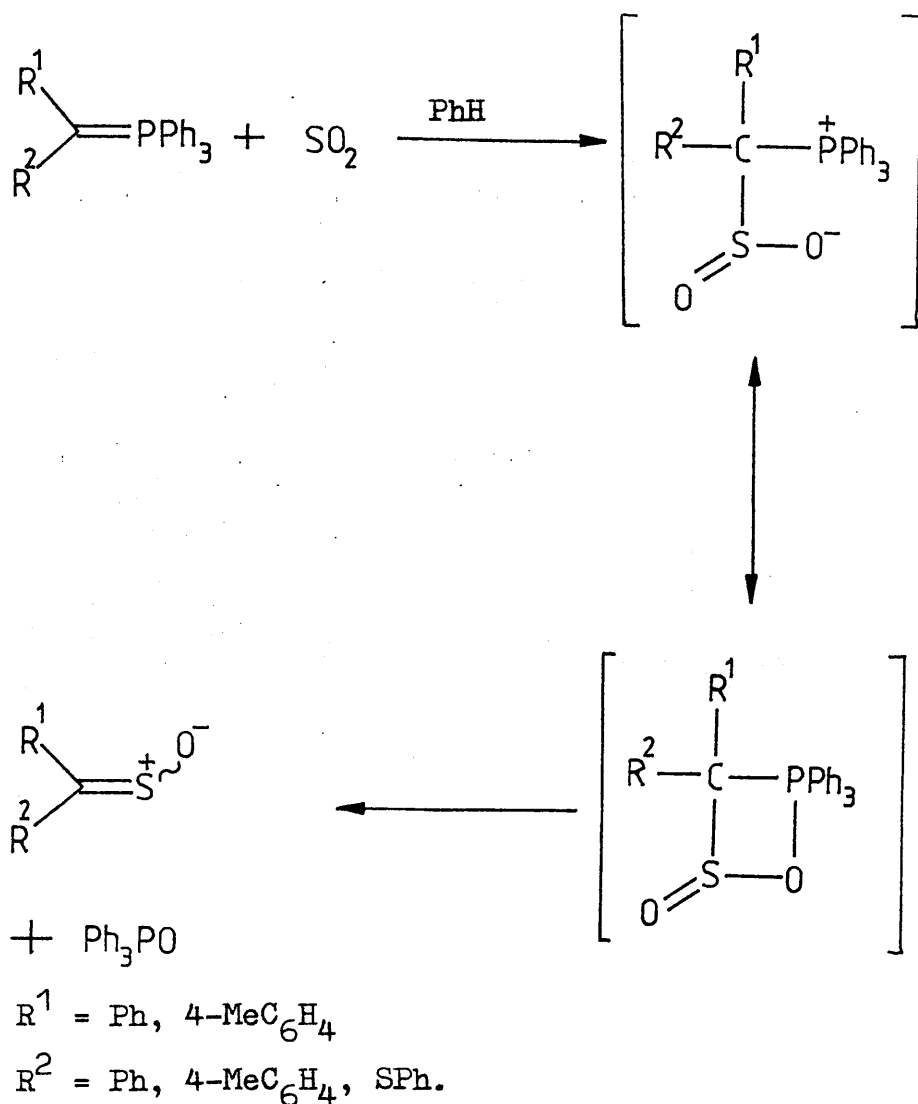
Ph_2S

$\text{C}_5\text{H}_5\text{N}$

Scheme 13.

(vi) Wittig alkylation of sulphur dioxide.

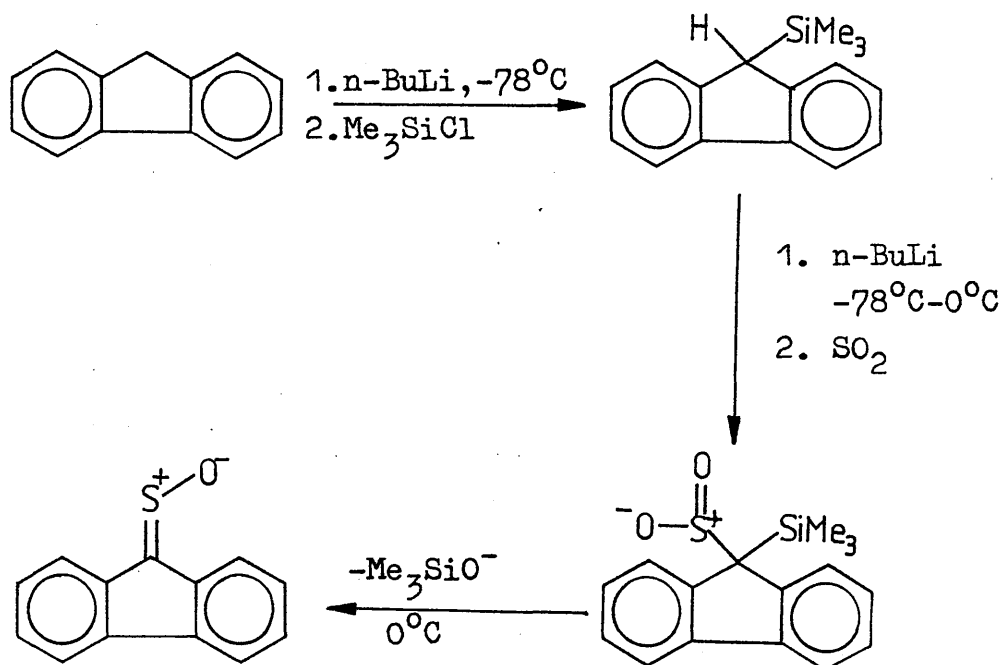
Zwanenburg et al.³⁴ showed that reaction of phosphonium ylids with an excess of sulphur dioxide in an apolar solvent gave the corresponding diarylsulphines. In analogy with the Wittig reaction it is assumed that the initial reaction of these stabilised ylids is with sulphur dioxide forming a sulphobetaine which then fragments to the sulphine and triphenylphosphine oxide (Scheme 14).



Scheme 14.

(vii) Alkylidenation of sulphur dioxide using α -silyl carbanions.

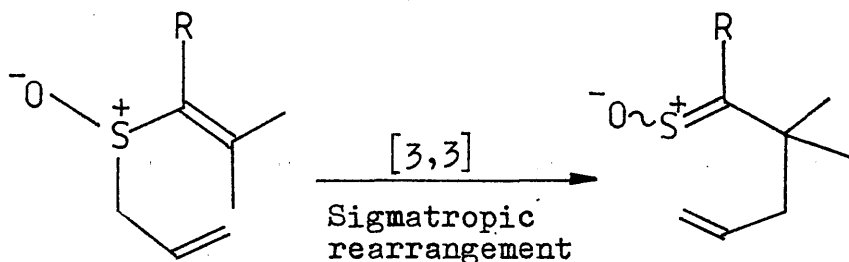
Zwanenburg et al.³⁵ also showed that a variety of sulphines can be produced by replacement of one oxygen atom in sulphur dioxide by an alkylidene group. Thus when α -silyl carbanions react with sulphur dioxide, the primary formed adduct, an α -silyl sulphinate, smoothly eliminates trimethylsilanolate to give the thiocarbonyl group (Scheme 15).



Scheme 15.

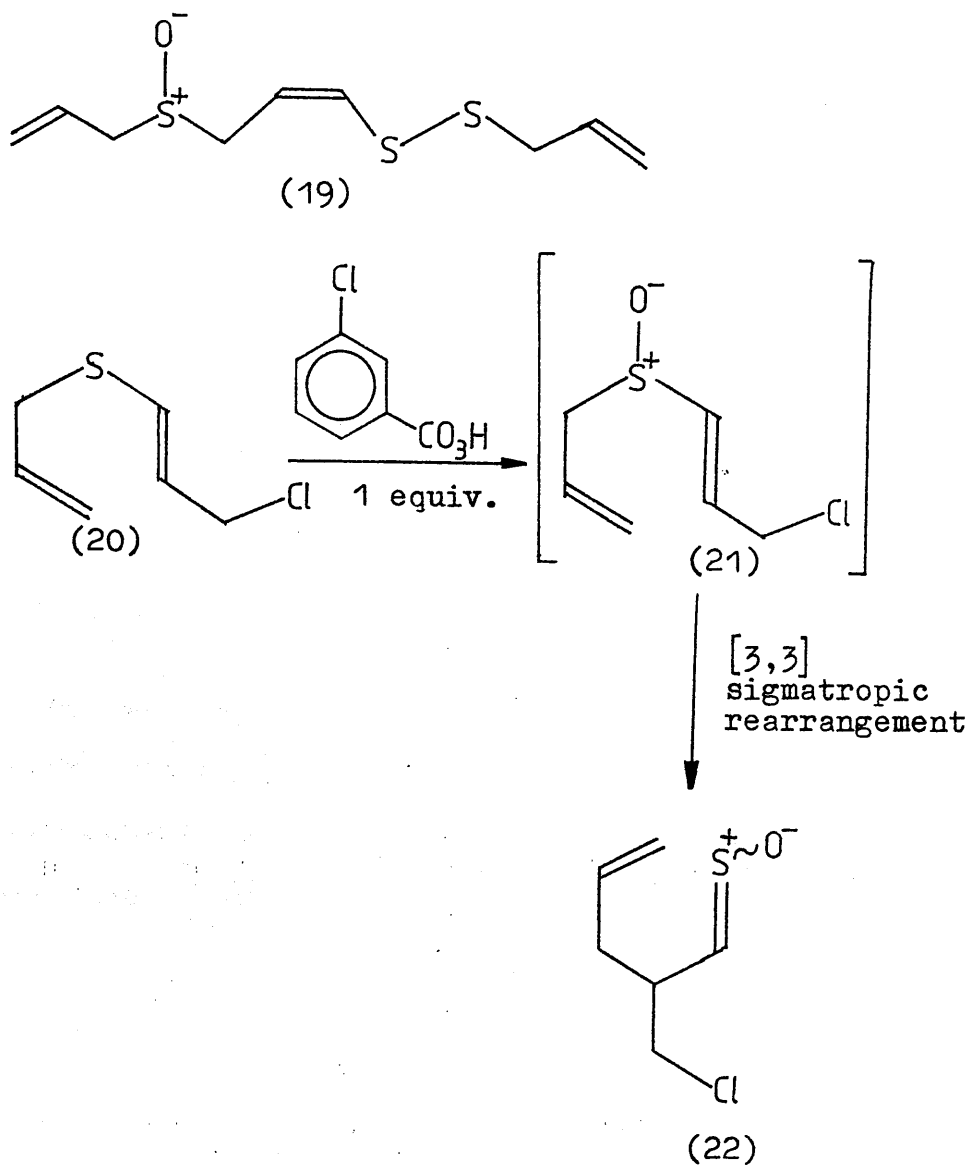
(ix) Sigmatropic rearrangement of allyl vinyl sulphoxides.

Hwu and Anderson³⁶ showed that γ, δ -unsaturated sulphines were readily obtained by [3,3] sigmatropic rearrangement of allyl vinyl sulphoxides. They were able to prove that in neutral solution, the accelerating effects of the charges in the zwitterionic sulphoxide group do not cancel, but instead this group significantly facilitates the rearrangement (Scheme 16).



Scheme 16.

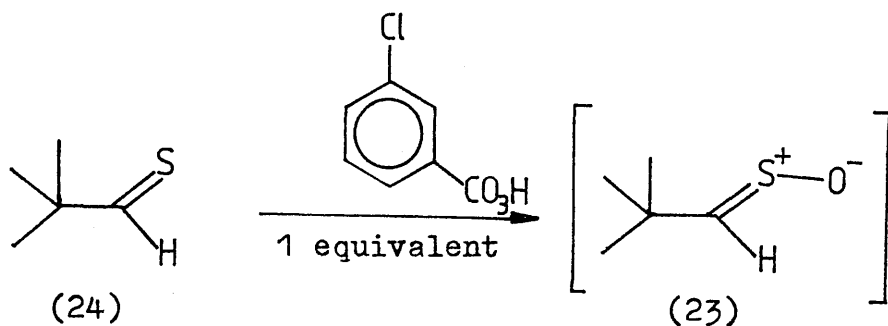
Block et al.³⁷ also isolated a sulphine formed by sigmatropic rearrangement whilst investigating the chemistry of compounds related to ajoene (19), a constituent of garlic (Allium sativum). Upon oxidation of the sulphide (20), they found the product to be not the sulphoxide (21), but instead the sulphine (22), formed by its rearrangement (Scheme 17).



Scheme 17.

Synthetic methods for production of thioaldehyde S-oxides.

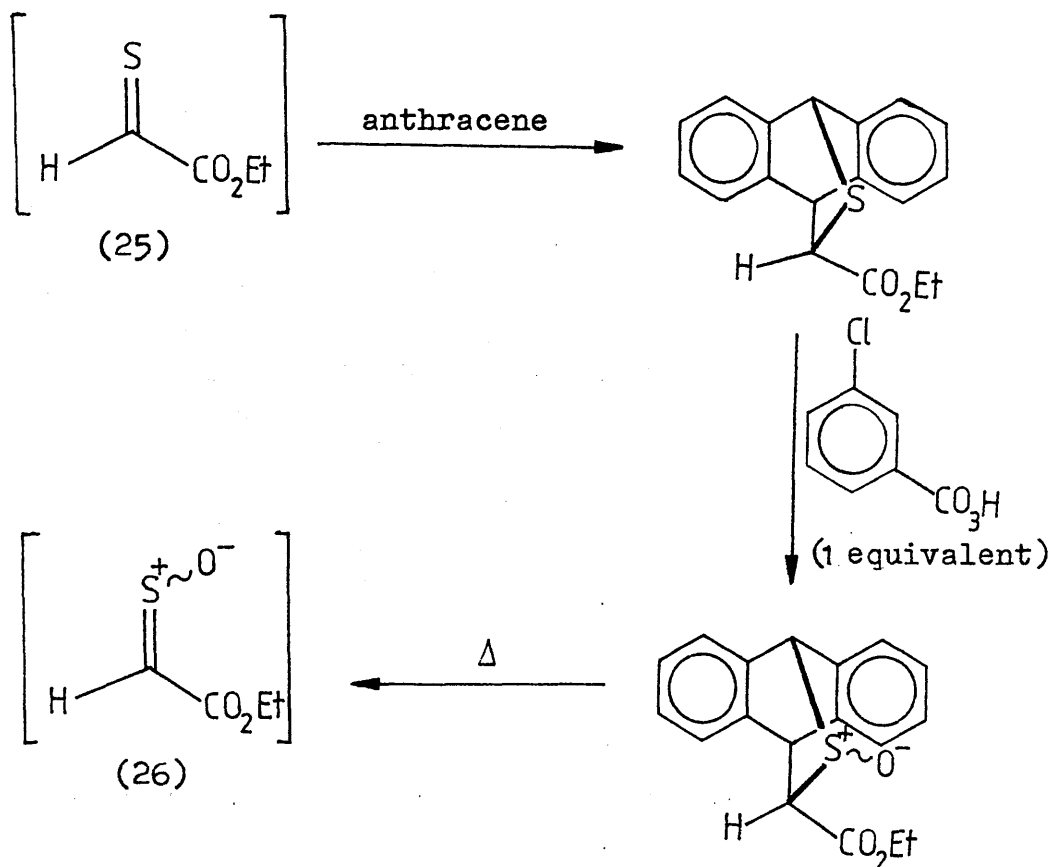
Usually, thioaldehyde S-oxides, the most reactive class of sulphines, are prepared either by direct oxidation^{17,38,39,40} or by elimination of hydrogen chloride from the corresponding sulphinyl chlorides^{6,41}. For example, Vedejs et al.³⁸ prepared the unstable sulphine (23) by direct oxidation of the sterically stabilised thioaldehyde (24) using 3-chloroperbenzoic acid (Scheme 18).



Scheme 18.

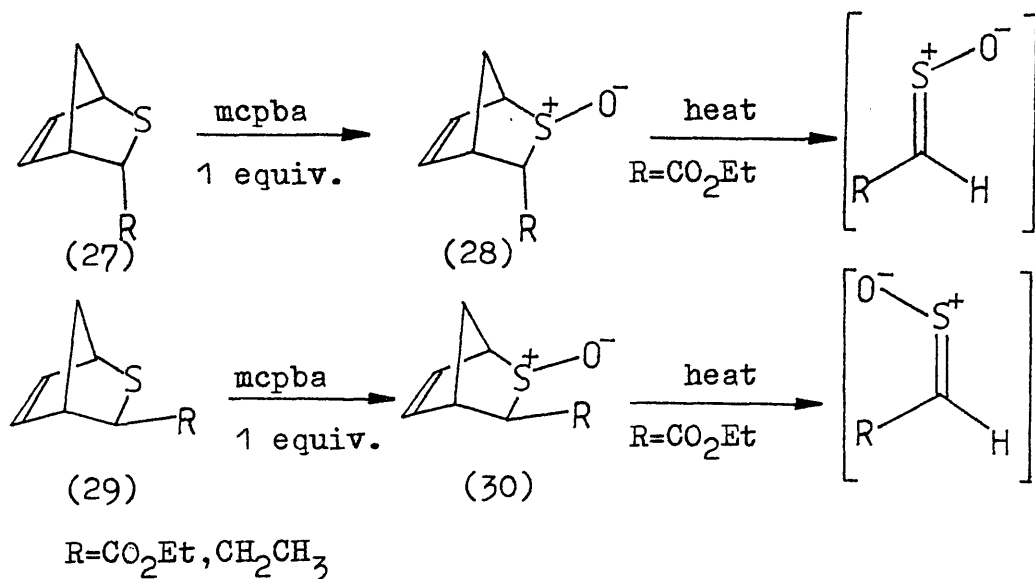
In general however, as thioaldehydes are transient species which readily dimerise or polymerise, the corresponding thioaldehyde S-oxides cannot be prepared in such a way. Kirby et al.³⁹ overcame this problem by generating these sulphines by retro-Diels-Alder cleavage of suitable cycloadducts. Thus they trapped the reactive thioaldehyde ethyl thioxoacetate (25) as Diels-Alder adducts with various cyclic dienes. The stable products could then be oxidised, to the corresponding sulfoxides, which were effectively cycloadducts of the sulphine ethyl thioxoacetate S-oxide (26), which could then be liberated thermally. The use of anthracene as the 'diene' is shown in Scheme 19.

Kirby et al.³⁹ and independently Block and Wall⁴⁰ found that oxidation of the sulphides (27) gave predominantly trans S-oxides (28), whereas oxidation of the sulphides (29) gave predominantly cis S-oxides (30). Thus, using this approach Kirby et al.³⁹ were able to



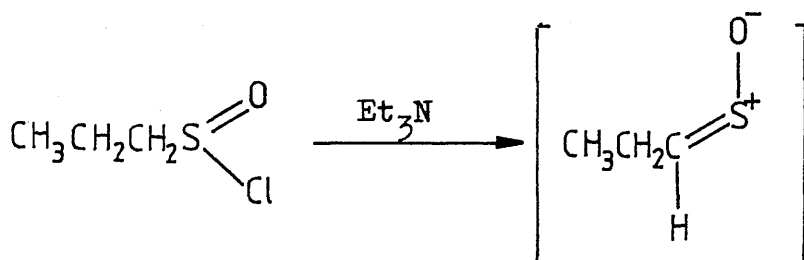
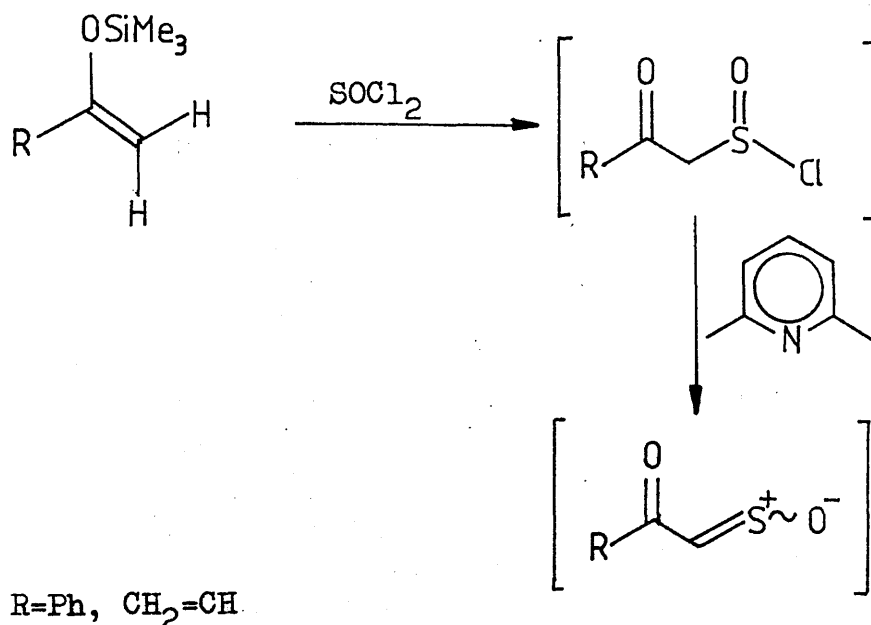
Scheme 19.

generate exclusively cis and trans sulphines in separate experiments (Scheme 20).



Scheme 20.

Zwanenburg et al.^{6,41} generated a number of α -oxo sulphines by base induced 1,2 dehydrochlorination of the corresponding sulphonyl chlorides, prepared by treatment of the appropriate silyl enol ethers with thionyl chloride. Commonly the base of choice was 2,6-lutidine (Scheme 21). Generally this method gave a mixture of cis and trans sulphines. In contrast, Block and Wall⁴⁰ found that when 1-propanesulphonyl chloride was treated with triethylamine the cis sulphine propanethial cis-S-oxide was generated exclusively.

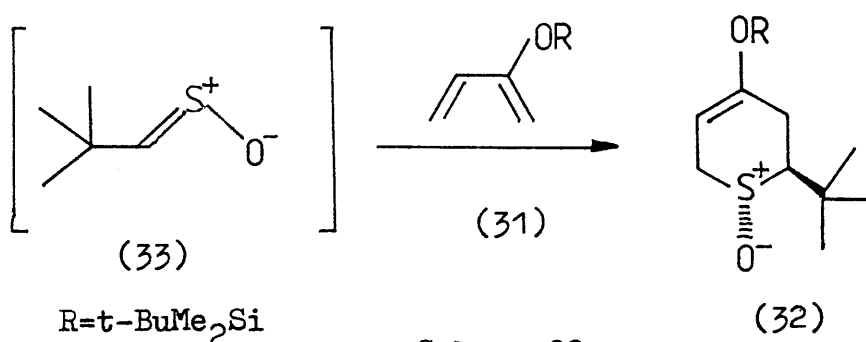


Scheme 21.

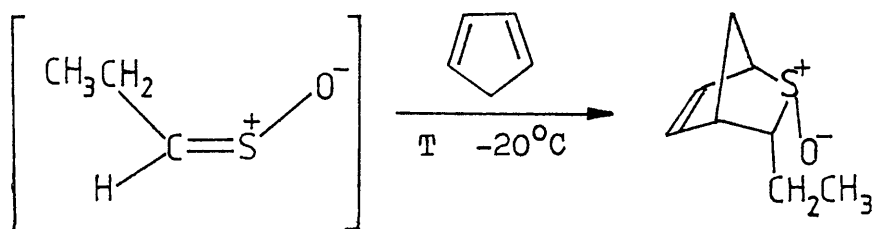
Cycloaddition reactions of sulphines.

The cycloaddition reaction with dienes and 1,3-dipoles is a well documented reaction of sulphines. A great variety of dienes react with differently substituted sulphines to give dihydropyran S-oxides^{4,42}. Many different types of 1,3-dipoles have also been found to react with sulphines^{4,5}.

Formation and identification of the cycloadduct of an unstable sulphine has been used to show the latter's presence as a reactive intermediate. For example Vedejs et al.³⁸ were able to prove the existence of the sulphine (23) formed by oxidation of the thioaldehyde (24) by trapping it as a Diels-Alder adduct with the diene (31) and identifying the product (32) (Scheme 22). Likewise, Block et al.⁴³ isolated the onion lachrymator, propanethial cis S-oxide, by trapping it at low temperatures using cyclopentadiene (Scheme 23).

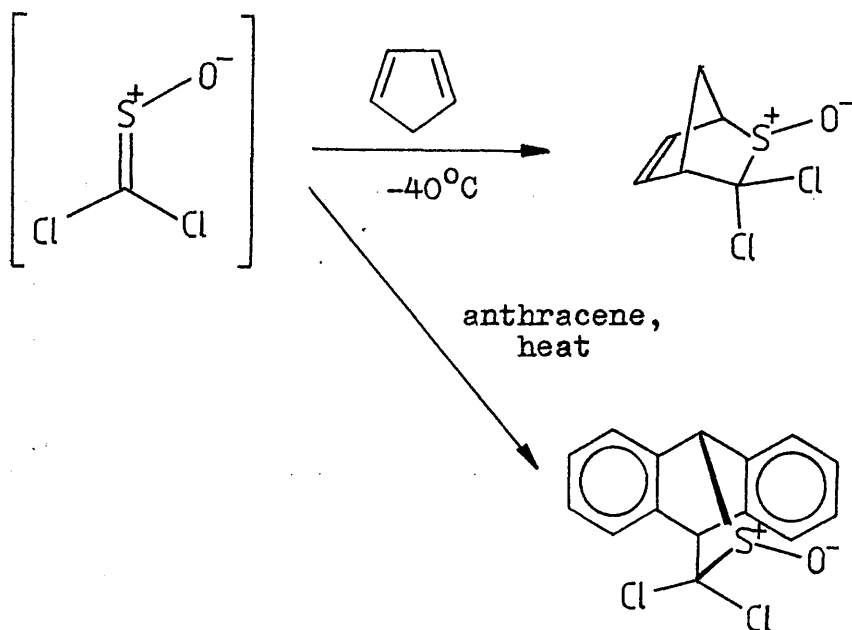


Scheme 22.



Scheme 23.

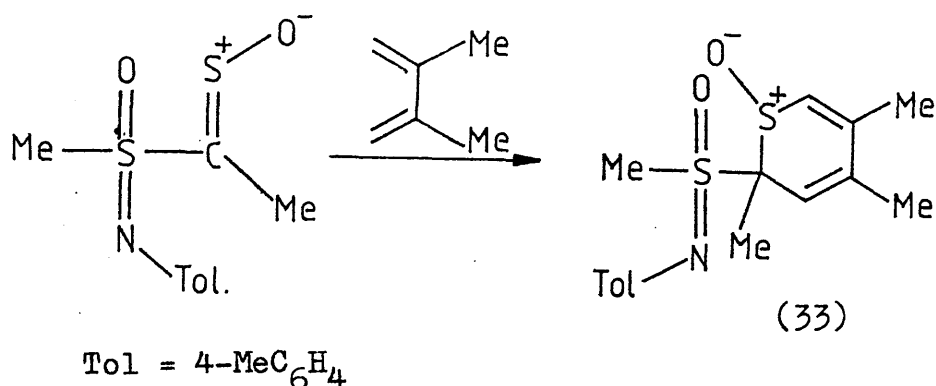
As expected, the dienophilicity of sulphines is dependent upon the substituents present. Electron withdrawing substituents, e.g. chlorine, enhance the reactivity. For example, Zwanenburg et al.⁴² showed that dichlorosulphine was highly reactive and readily formed adducts with both cyclopentadiene and anthracene (Scheme 24). However, Block⁴⁴ showed that even simple alkyl sulphines, such as methanethial S-oxide, react exothermically with cyclopentadiene.



Scheme 24.

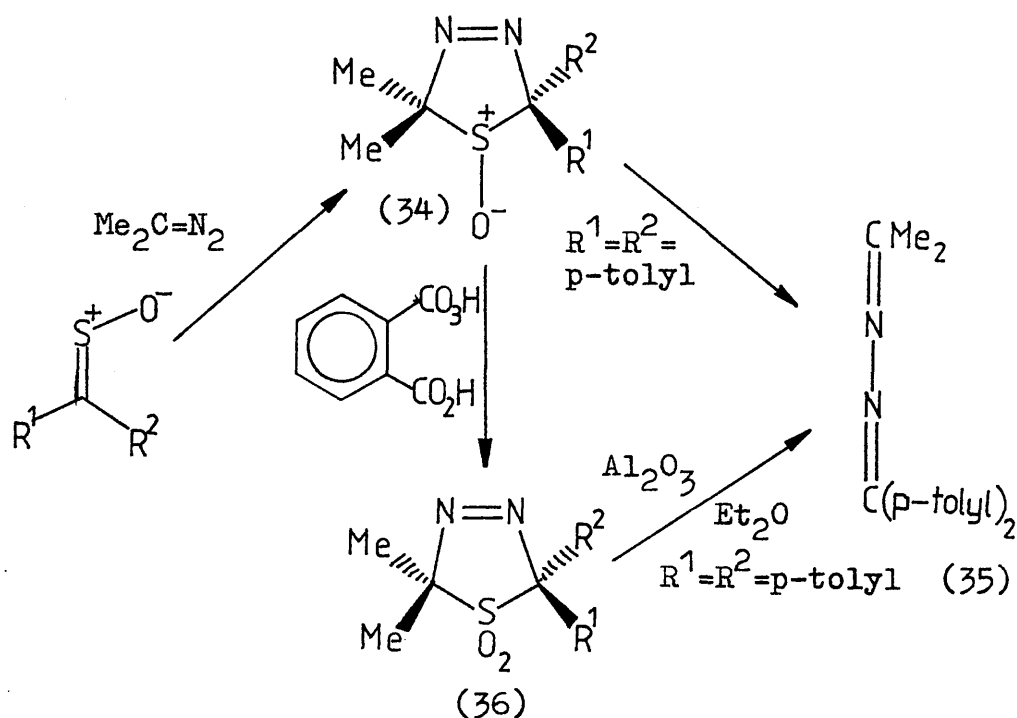
Zwanenburg and Hermans⁴⁵ showed that very high asymmetric induction could be achieved using chiral sulphines. With sulfoximino sulphines, which have the inducing chiral centre in close proximity to the sulphine function, diastereomeric excesses of near 100% were usually found (Scheme 25). From an analysis

of the crystal structure of the adduct (33), they suggested that the steric hindrance exerted by the N-alkyl group of the sulfoxime functions was responsible for the high diastereoselectivity observed.



Scheme 25.

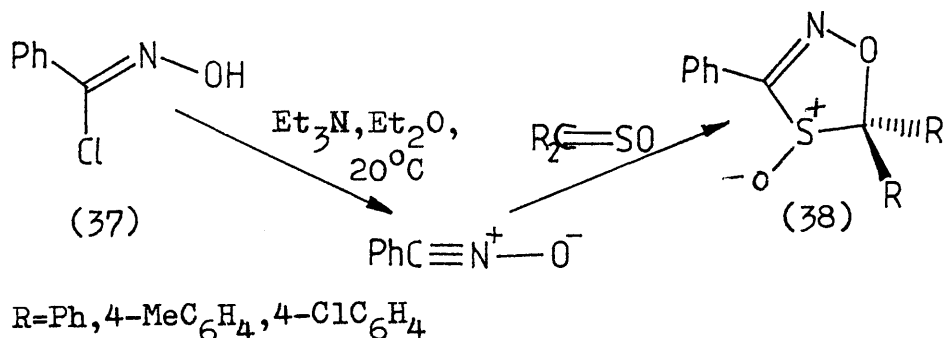
Much attention has been given to the reactions of sulphines prepared by peracid oxidation of the corresponding thiones with diazo compounds. Aromatic and aliphatic sulphines react with 2-diazopropane in a regiospecific and stereospecific manner to give Δ^3 -1,3,4-thiadiazoline S-oxides³⁴, usually in good yields. Bonini et al.⁴⁶ unambiguously established the orientation of cycloaddition by photochemical extrusion of sulphur monoxide from the product (34) giving the unsymmetrical azine (35). This azine was likewise obtained by smooth elimination of sulphur dioxide from the sulphone (36) obtained upon oxidation of (34) (Scheme 26).



$\text{R}^1, \text{R}^2 = \text{Ph}, 4\text{-MeC}_6\text{H}_4, \text{Cl}, \text{SPh}$

Scheme 26.

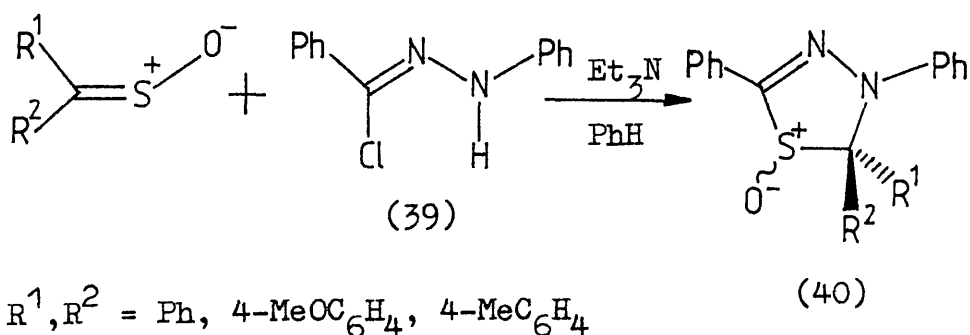
The cycloaddition of 2-diazopropane with geometrically isomeric pairs of different types of sulphines produces distinct diastereoisomeric products⁴⁷. Consequently, the stereochemistry of the sulphine is retained in the cycloadduct, indicative of a concerted cycloaddition process. Likewise cycloaddition of diarylsulphines with benzonitrile



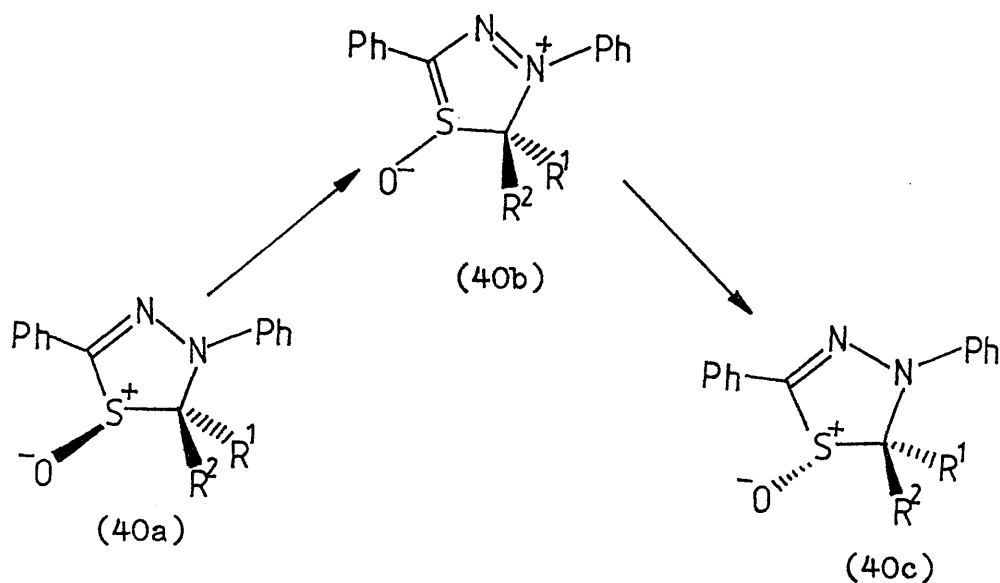
Scheme 27.

oxide, generated in situ from the precursor (37), in almost all cases led to 1,4,2-oxathiazole S-oxides (38) with the same stereochemistry⁴⁸ (Scheme 27).

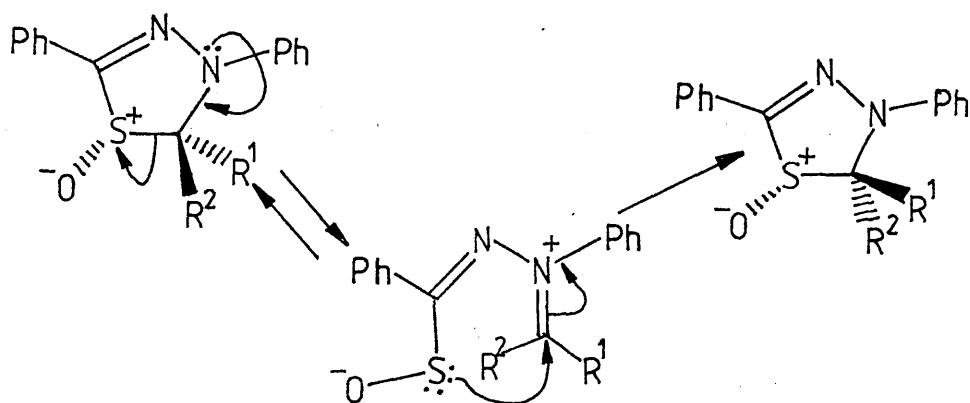
In remarkable contrast however cycloaddition of diphenylnitrilimine, generated in situ from N-(α -chlorobenzylidene)-N'-phenylhydrazine (39) and triethylamine, with geometrically isomeric sulphines was not stereospecific^{49,50} (Scheme 28). Isomerisation of sulphines in the presence of triethylamine was indeed observed, however at a rate much slower than the cycloaddition to give (40), since sulphines recovered from incomplete reaction had the original configuration. Thus isomerisation prior to cycloaddition is not a likely explanation for the non-stereospecificity. Pyramidal inversion of the sulfoxide function via a transition state (40b), planar about sulphur (Scheme 29) also seems unlikely since sulfoxides in general are configurationally quite stable. Bonini et al.⁵⁰ were able to show that the stereomutation could be accounted for by the ring-opening-ring-closure mechanism shown in Scheme 30.



Scheme 28.



Scheme 29.

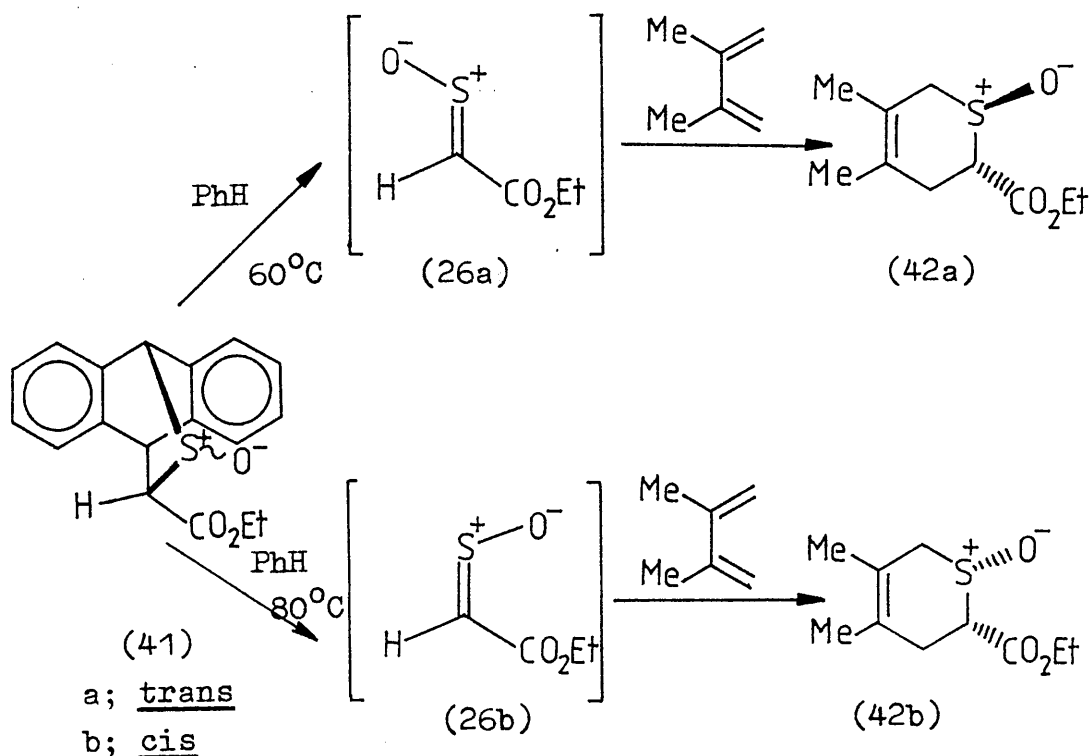


Scheme 30.

Retro-Diels-Alder reactions.

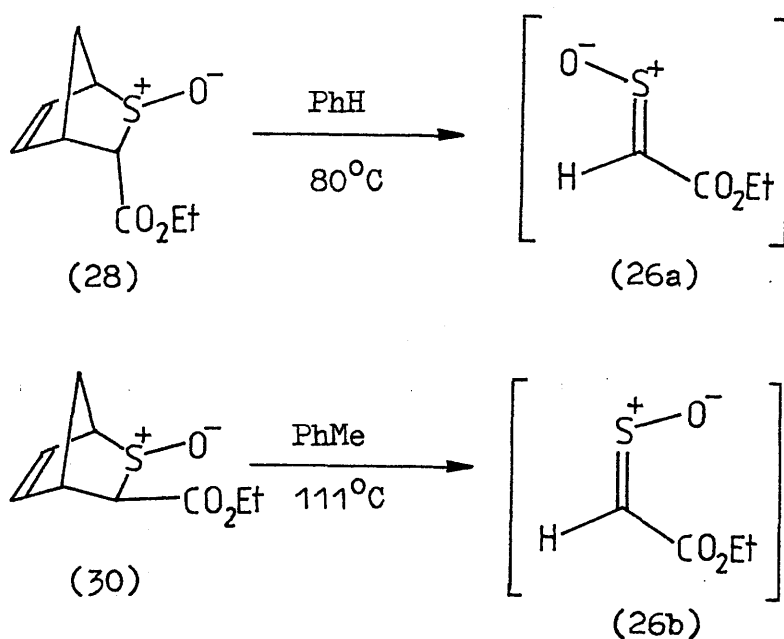
Recently it has been shown that sulphines can be generated thermally by retro-Diels-Alder reactions from appropriate precursors. Elasser and Sundermeyer^{6,51} reported the preparation of the thioketone oxide $(\text{CF}_3)_2\text{C}=\text{SO}$ by thermolysis of its anthracene adduct at 150°C . Sulphines of thioaldehydes have also been generated by this method. Valee *et al.*²³ generated the parent sulphine methanethial S-oxide by thermolysis of

its anthracene adduct using the flash vacuum pyrolysis technique (925°K , 10^{-6} torr). Kirby *et al.*³⁹ showed that the highly reactive sulphine ethyl thioacetate S-oxide could be released thermally at much lower temperatures from its anthracene cycloadduct. Furthermore they were able to show that the isomeric cis and trans sulphoxides released the corresponding sulphines at different temperatures. Thus, whereas in benzene at 60°C , the sulphine ethyl thioacetate trans-S-oxide (26a) was released from anthracene, the cis sulphoxide adduct was recovered unchanged. In benzene at 80°C however the cis-sulphine (26b) was liberated. When the sulphines were trapped in turn with 2,3-dimethylbuta-1,3-diene the stereochemistry of the anthracene adduct precursors (41) was retained in the butadiene adduct products (42a) and (42b) (Scheme 31).



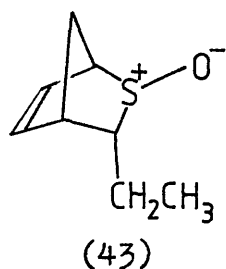
Scheme 31.

Likewise Kirby et al.³⁹ showed that only the 'cyclopentadiene' trans-sulphoxide (28) dissociated in refluxing benzene releasing the trans-sulphine (26a). The cis-sulphoxide (30) was stable in refluxing benzene but dissociated in refluxing toluene releasing the cis-sulphine (26b) (Scheme 32).

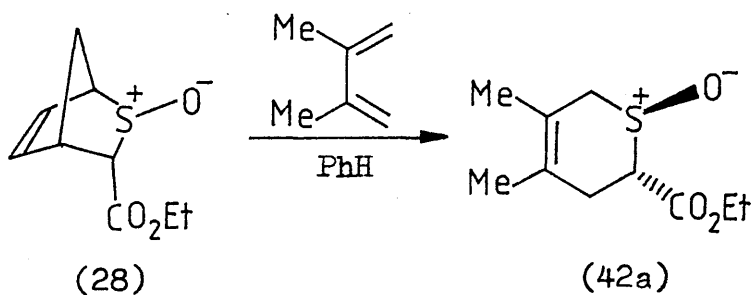


Scheme 32.

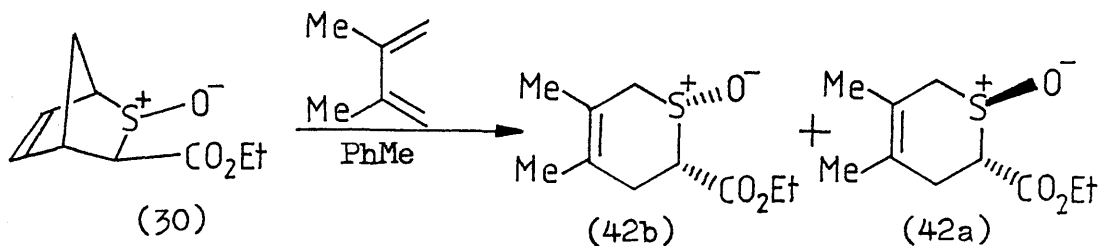
In contrast, Block and Wall⁴⁰ report that the sulphoxide (43) is stable for extended periods in refluxing toluene, although they did not heat this oxide in the presence of a sulphine 'trap', e.g. dimethylbutadiene. Thus the rate of release of thioaldehyde S-oxides is dependent upon both their stereochemistry and the nature of their α -substituents.



In all transfer reactions to date involving trans-sulphines, transfer has been shown to be stereospecific with the stereochemistry of the precursor being retained in the product. Thus the trans-S-oxide (28) was converted to the product sulfoxide (42a) with complete retention of stereochemistry (Scheme 33). In some transfer reactions involving cis-sulphines, the stereochemistry of the precursor is not fully preserved in the product. For example, the cis-S-oxide (30) was converted into a mixture of the two isomeric S-oxides (42a) and (42b) in the ratio (42b):(42a) 1:2 and 1:1 in separate experiments (Scheme 34).

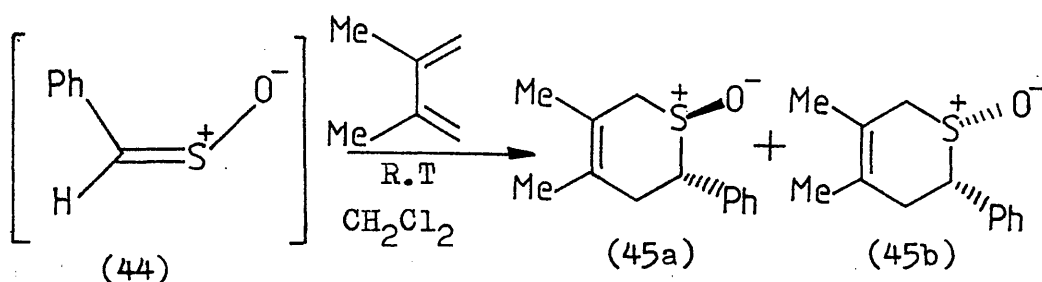


Scheme 33.



Scheme 34.

Bonini et al.¹⁷ found that when they allowed the cis-sulphine (44), which was stable enough to be isolated at low temperatures, to react with 2,3-dimethylbuta-1,3-diene at room temperature, they also observed slow formation of a mixture of the S-oxides (45a) and (45b) in the ratio (45a):(45b) = 3.3:1 (Scheme 35). The corresponding trans-sulphine was not available for comparison.



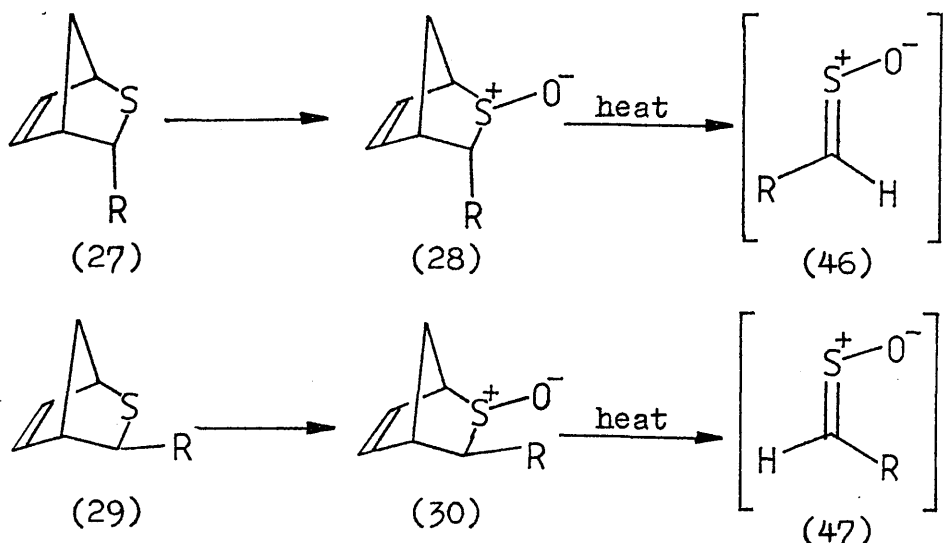
Scheme 35.

At the outset of the present research the literature contained only a few examples of the generation of sulphines by retro-Diels-Alder reactions. Thus Zwanenburg's comprehensive 1982 review⁴ lists ten methods for sulphine synthesis but records no example of retro-Diels-Alder cleavage, potentially a powerful method for liberating unstable sulphines under mild, 'clean' conditions. We planned therefore to explore more thoroughly the preparative scope of the method and to clarify the striking dependence of the dissociation

rates of cycloadducts on (a) the α -substituent of the derived sulphine, and (b) the stereochemistry of the precursor sulphoxide. Further, we wished to investigate the stereochemical outcome of the thermal transfer of trans and cis sulphines from the precursor to the product diene. The results of our research are now presented.

2. Discussion of results.

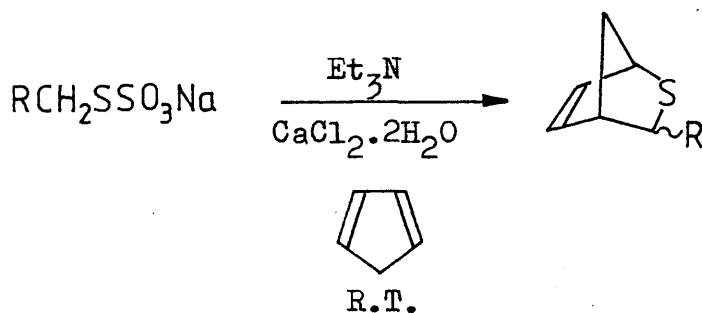
Preparation of cyclopentadiene thioaldehyde adducts.



Scheme 36.

In a continuation of the work of Lewis⁵² various thioaldehyde adducts of cyclopentadiene were prepared. It was hoped that these would serve as precursors to cis (30) and trans (28) sulfoxides and hence cis (47) and trans (46) sulphines (Scheme 36), thereby extending the two earlier examples (28; R=CO₂Et) and (30; R=CO₂Et). Thus endo and exo mixtures of the adducts of cyclopentadiene with thioxoacetophenone, (52) 4-bromothioxoacetophenone, (53) 4-nitrothiobenzaldehyde, (54) and thioxoacetonitrile, (55); were prepared by the method of Kirby et al.⁵³ (Scheme 37) and identified by ¹H n.m.r. spectroscopy. This involved treating the

Bunte salts (48)-(51), in methanol, with 1.2 equivalents of triethylamine in the presence of one equivalent of calcium chloride dihydrate and 1.2 equivalents of cyclopentadiene. (The calcium chloride was present to remove the nucleophilic sulphite ion from the reaction mixture). Very good yields of adducts (52)-(55) were obtained at room temperature. The endo:exo ratios, determined by ^1H n.m.r. integration of the β -H signals (Table 1), were found to be as reported in the literature⁵³. In the case of (52) and (53), the endo and exo isomers were separable by chromatography. However the endo and exo isomers of (54) and (55) were not separable.



R = C ₆ H ₅	(48)	(52)
4-BrC ₆ H ₄ CO	(49)	(53)
4-NO ₂ C ₆ H ₄	(50)	(54)
CN	(51)	(55)

Scheme 37.

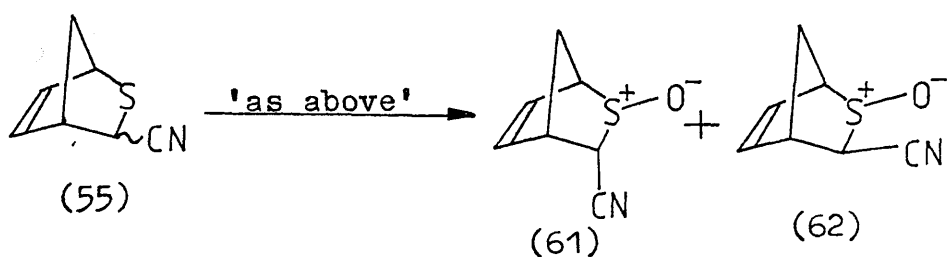
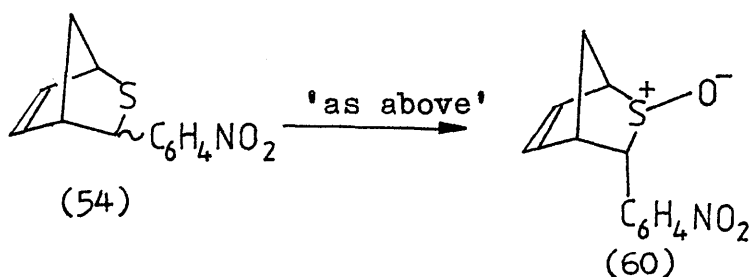
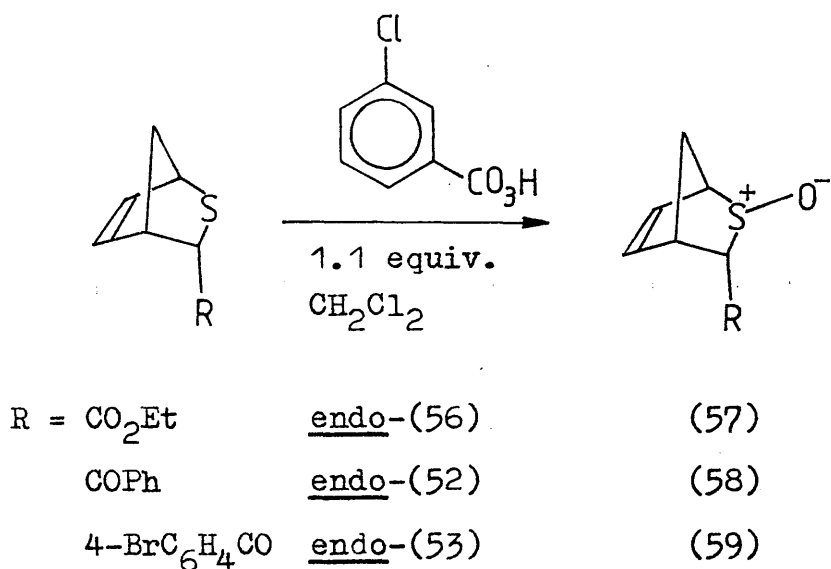
Table I. Endo:exo ratios (^1H n.m.r. analysis) for cyclopentadiene thioaldehyde adducts obtained at room temperature.

R	<u>endo</u>	<u>exo</u>
COPh (52)	7	3
4-BrC ₆ H ₄ CO (53)	8	3
4-NO ₂ C ₆ H ₄ (54)	7	1
CN (55)	2	1

Preparation of trans sulphoxides from endo sulphides.

The sulphides endo-(52), endo-(53), and the mixtures (54) and (55), were oxidised in dichloromethane at room temperature using 1.1 equivalents of 3-chloroperbenzoic acid to give respectively the trans sulphoxides (57)-(61) (Scheme 38). The trans stereochemistry, deduced from analysis of their ^1H n.m.r. spectra, will be discussed later. As observed by Kirby et al.³⁹ for the oxidation of (56) to give (57), (58) and (59) were isolated in good yield as the sole sulphoxide products identifiable from the ^1H n.m.r. spectra of the reaction mixtures after workup. Oxidation of the sulphide mixture (54) gave (60) in 85% yield as the sole identifiable product after crystallisation. It appears that the small amounts of exo-(54) are lost upon oxidation. Oxidation

of the sulphide mixture (55) gave (61) as the main sulphoxide product. However, after chromatographic purification of the complex mixture so obtained, the ^1H n.m.r. spectrum showed that traces of a minor sulphoxide, presumably (62), had also been formed. The other by-products were not identified. Upon crystallisation of the chromatographed mixture, (61) was obtained pure in 38% yield.



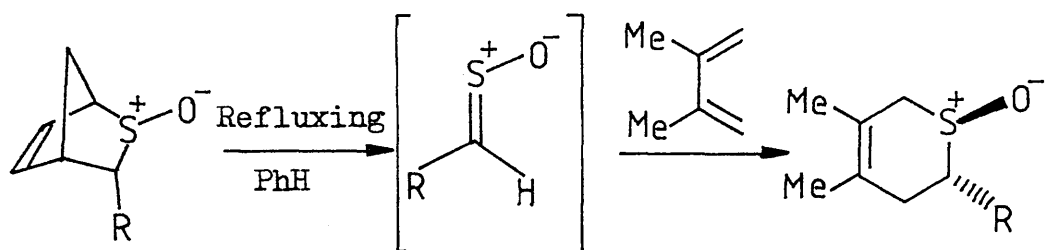
+ other minor products

Scheme 38.

Thermal 'transfer' of trans-sulphines from cyclopentadiene to dimethylbutadiene.

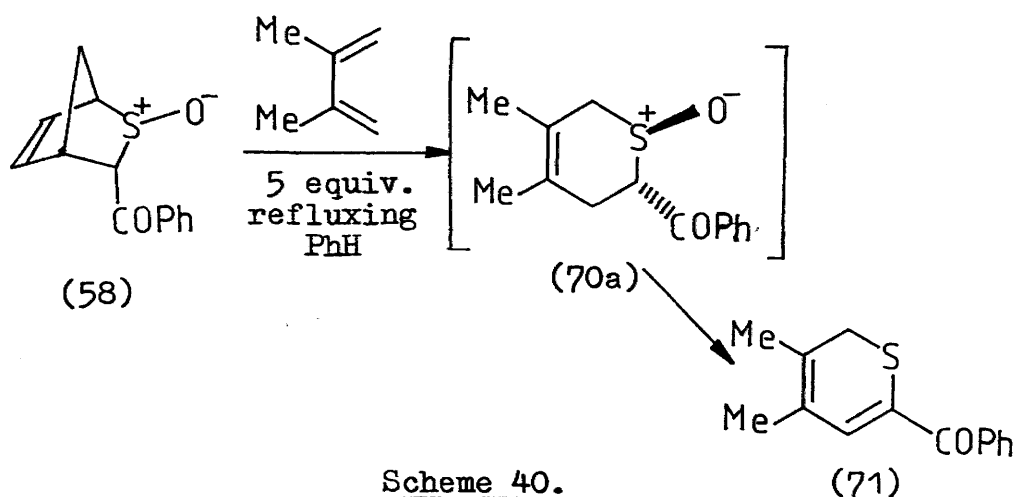
In order to generate the trans sulphines (63)-(66) from (58)-(61), each was heated with 2,3-dimethylbuta-1,3-diene (5 mol equiv.) in refluxing benzene under nitrogen for the times indicated in brackets in Scheme 39. In agreement with the earlier experiment³⁹ with the ethyl ester (57) the only products obtained from the precursors (59)-(61) were the trans sulfoxides (67)-(69) in yields of 62-92% (Scheme 39). The structures and trans configurations were deduced from various chemical studies and the ¹H n.m.r. spectra; these will be discussed later. The product obtained from the benzoyl precursor (58), however, had no characteristic infrared sulfoxide S-O stretching band near 1,050 cm⁻¹ and it was deduced from its ¹H n.m.r. spectrum [δ (CDCl₃) 1.67 and 1.71 (2xs, 4- and 5-CH₃), 3.30 (m, 6-H₂), 6.73 (s, 3-H), and 7.40-7.60 and 7.86-8.02 (2xm, ArH)] to be the thiapyran (71). This was presumably formed from (70a) via a Pummerer rearrangement brought about by acidic impurities in the reaction medium (Scheme 40). Zwanenburg et al.⁴¹ obtained similar ¹H n.m.r. data for the 2-(2-naphthoyl) analogue of (71). Lewis⁵² also observed a similar result when he heated (72) with sodium perborate in acetic acid to obtain not the sulfoxide (42) but instead the

thiapyran (73) (Scheme 41). When however, the benzoyl derivative (58) was rigorously purified then heated with butadiene, the trans sulphoxide (70a) was isolated as the sole product (84%). Since the 4-bromobenzoyl sulphoxide (59) was found to be easier to purify than the simple benzoyl sulphoxide (58), (59) was preferred for further 'transfer' experiments of this type. The fact that in all cases trans butadiene adducts were isolated, showed that, as with the earlier experiment³⁹ with the ethyl ester derivative (57), the trans sulphines (63)-(66) had been liberated and recaptured with complete retention of stereochemistry. For the transfer of the trans sulphines (63)-(65), reaction was complete within 10h. Transfer of trans cyano sulphine (66) however was not complete until after 24h. More detailed reaction times were recorded for the transfer of a series of trans sulphines, including (64) and (65), from anthracene; these will be discussed later.

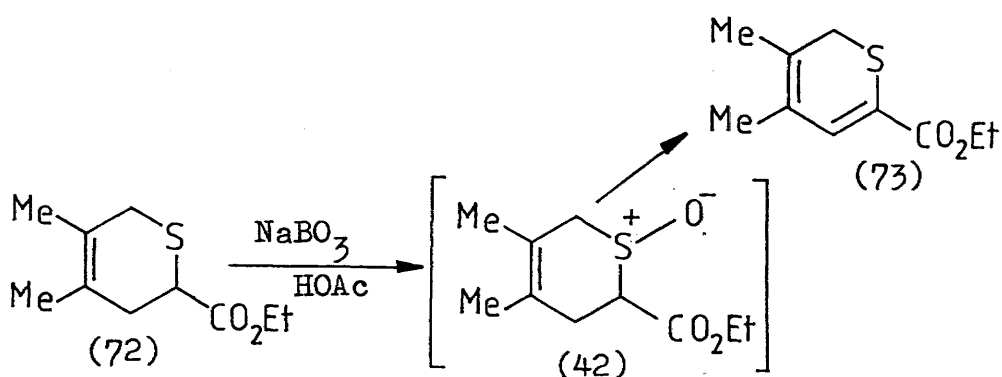


R = C ⁶ H ₅ CO	(58)	(63)	(70a)	(10h)
4-BrC ⁶ H ₄ CO	(59)	(64)	(67a)	(10h)
4-NO ₂ C ⁶ H ₄	(60)	(65)	(68a)	(10h)
CN	(61)	(66)	(69a)	(24h)

Scheme 39.



Scheme 40.

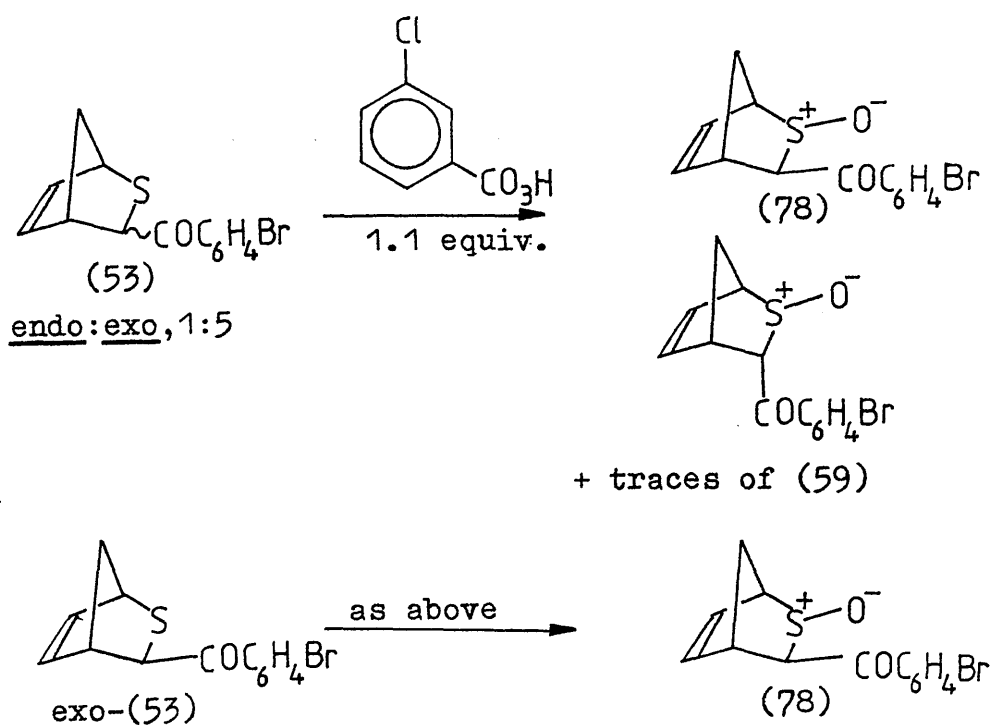


Scheme 41.

The gross structures of the sulphine cycloadducts (67)-(70) of dimethylbutadiene were verified by their synthesis by oxidation of the corresponding sulphides (74)-(77), prepared by the Bunte salt method⁵³, using 3-chloroperbenzoic acid in dichloromethane at room temperature. In each case, the products obtained in the transfer experiments (Scheme 39), were identical spectroscopically with the major sulphoxides formed by oxidation of the corresponding sulphides. The ratio of sulphoxides formed upon oxidation of the sulphides (74)-(77) and experiments to determine their stereochemistry will be discussed later.

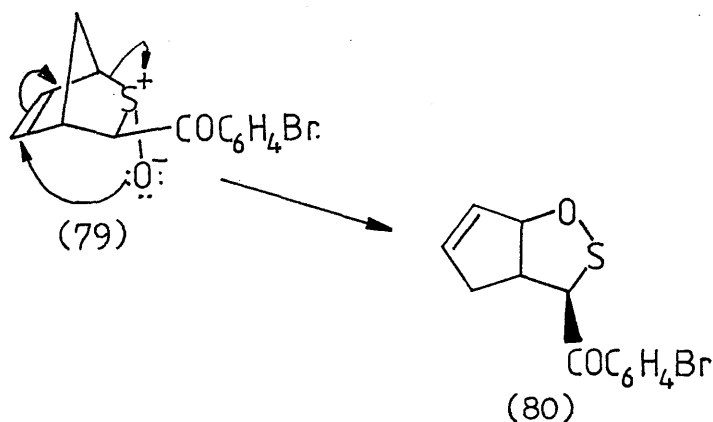
Preparation of cis sulphoxides from exo cyclopentadiene cycloadducts.

As stated earlier, the 4-bromobenzoyl cycloadduct exo-(53) was obtained by separation of the endo:exo mixture (53). This exo sulphide was also obtained as the major product by heating the 'kinetic' mixture of adducts (53) in refluxing toluene until thermodynamic equilibrium was attained. In this way, an exo-rich mixture, endo:exo ratio 1:5, was obtained. Oxidation of the exo sulphide, exo-(53) using 3-chloroperbenzoic acid in dichloromethane at room temperature gave the cis sulphoxide (78); oxidation of the equilibrated sulphide mixture (53) gave mainly (78) together with traces of the trans sulphoxide (59), which were lost upon repeated crystallisation (Scheme 42).



Scheme 42.

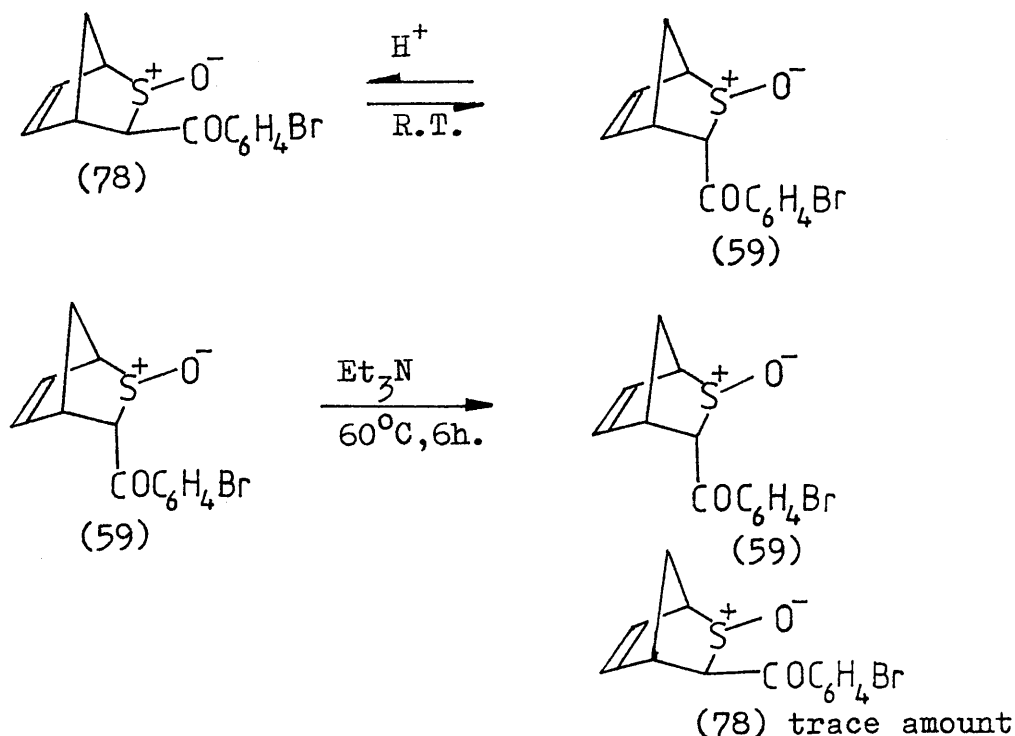
The fact that in (78), formed by oxidation of exo-(53), the sulfoxide oxygen has been introduced preferentially syn to the bulky keto substituent is surprising. It may be that approach of the oxygen to the otherwise sterically more accessible endo position is being prohibited by the repulsive effect of the π -cloud of the C=C bond. It would be expected that the endo sulfoxide (79) if formed at all, would be unstable, rearranging readily to give the bicyclic sultene (80) in an analogous manner to the process observed by Block and Wall⁴⁰ (Scheme 43). However there was no indication that this had happened, although the yield of the cis sulfoxide (78), 68%, was slightly less than that (76%) of the trans isomer (59) obtained by oxidation of the endo sulphide endo-(53).



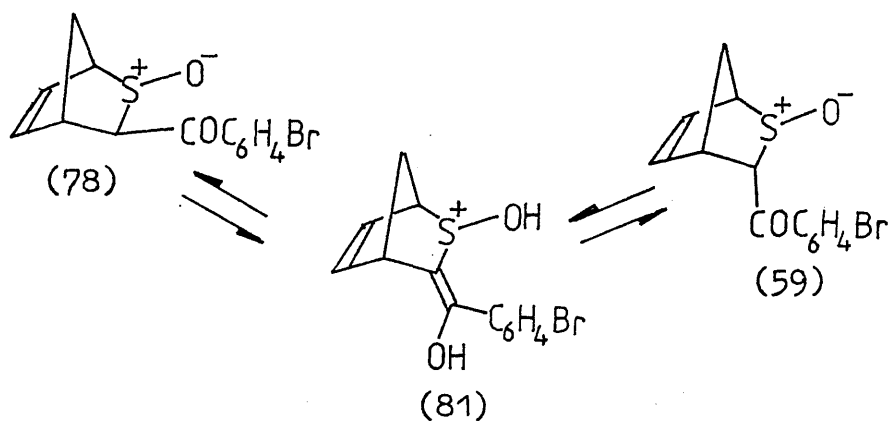
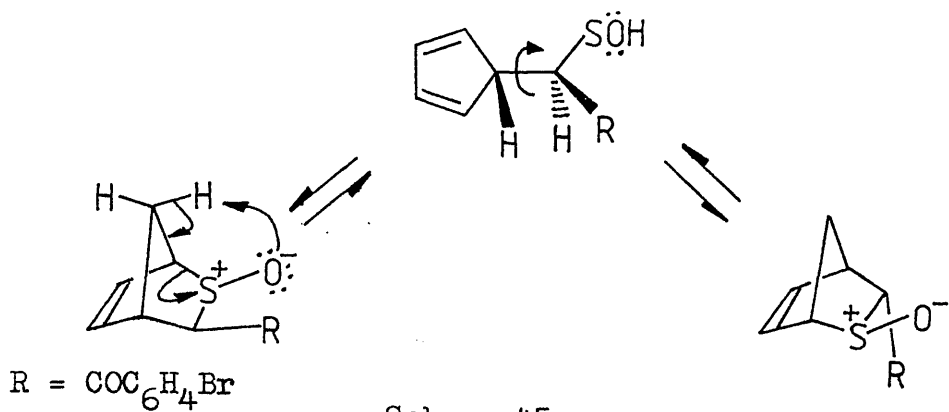
Scheme 43.

Although the trans sulfoxide (59) could be purified on a short silica column using ethyl acetate - light petroleum (1:4) as elutant, purification of (78)

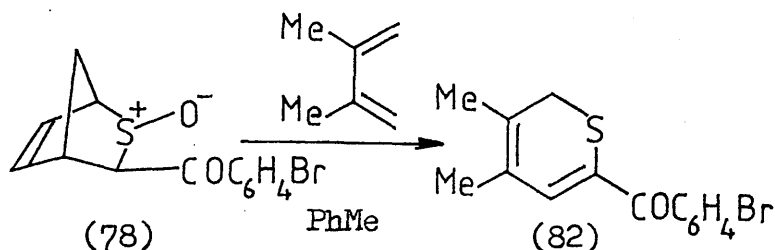
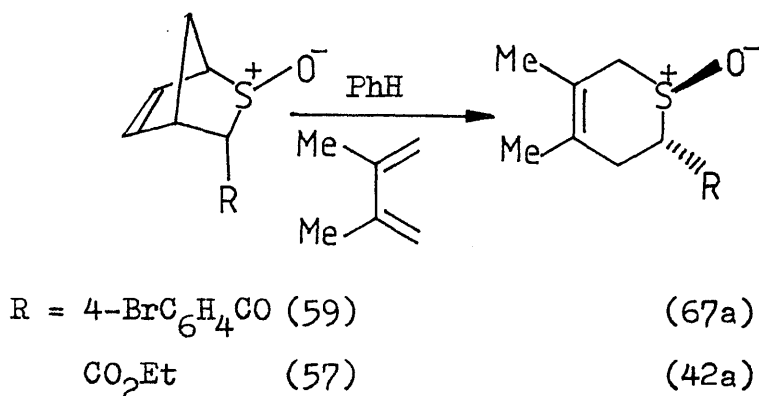
on both silica and fluorosil using the same solvent system led to unexpected epimerisation at C-3 at room temperature giving a mixture of (59) and (78) in the ratio (78):(59) 2:1 and 1:1 on separate occasions. However when (59) was heated with one equivalent of triethylamine in benzene at 60°C for 6h, only very small amounts of (78) were detected in the dark coloured reaction mixture (Scheme 44). Conversion of (78) to (59) might arise by a pericyclic mechanism (Scheme 45), however this seems unlikely since (78) was recovered unchanged after heating in refluxing benzene for 8h along with 5 equiv. of 2,3-dimethylbuta-1,3-diene. It seems probable therefore that (78) is converted into (59) by acid-catalysed epimerisation via the enolate (81) (Scheme 46).



Scheme 44.



As discussed earlier, the trans sulfoxide (59) reacted to give (67a) with complete retention of stereochemistry, when heated in refluxing benzene with five equivalents of 2,3-dimethylbuta-1,3-diene. In contrast, when the cis sulfoxide (78) was similarly treated, it was recovered unchanged. When the same experiment was carried out using toluene in place of benzene, the ¹H n.m.r. spectrum of the dark reaction mixture showed that all (78) had reacted and peaks e.g. [δ(CDCl₃), 3.33 (m, 6-H) and 6.73 (s, 3-H)] corresponding to the thiapyran (82) were observed along with those from other, minor products, which were not identified (Scheme 47).

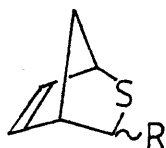
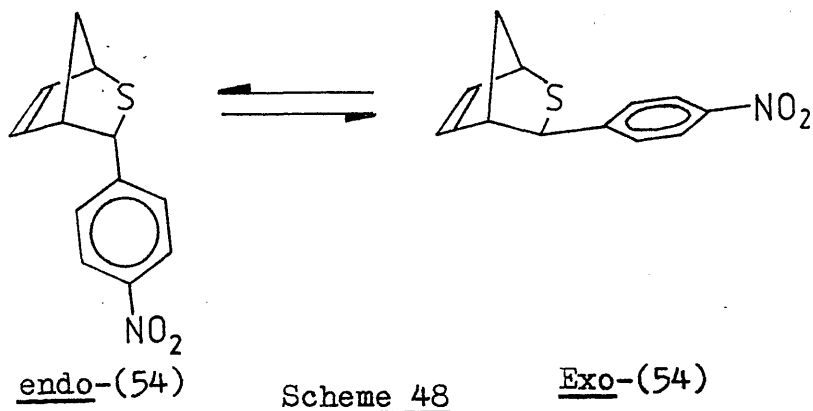


Scheme 47.

These experiments provide another example of the greater resistance of cis sulfoxide adducts towards thermolysis as compared with their trans analogues. Lewis⁵² found similar behaviour in experiments with the ethyl ester analogues (57) and (83).

In order to generate other cis sulphines it was first required to make the appropriate cis sulfoxide precursors by oxidation of the corresponding exo sulphides. Thus in an attempt to form the exo 4-nitrophenyl sulphide exo-(54), the sulphide mixture (54) was refluxed in benzene. After one hour the original 'kinetic' ratio of endo:exo sulphides was changed from 7:1 to 2:1 (Scheme 48). However the

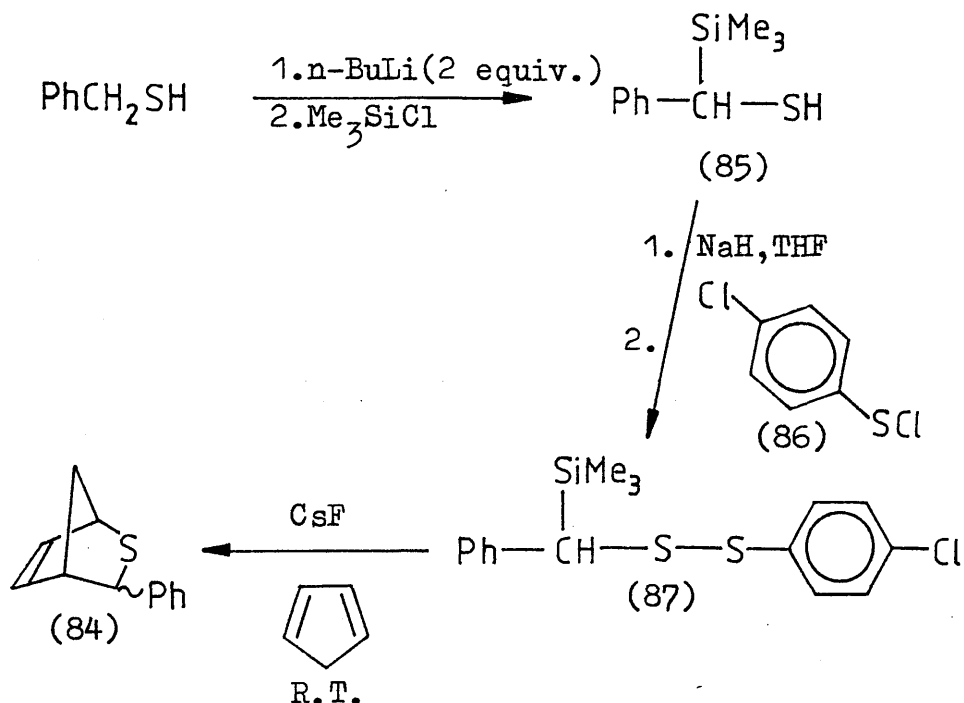
ratio was unchanged after a further 2h. Unfortunately, it was not possible to separate this mixture. Also, sulfoxides are more difficult to separate chromatographically than the corresponding sulphides. The required cis sulfoxide could not therefore be prepared. The equilibration result is surprising as it would be expected that the bulky nitrophenyl substituent would be more stable in the exo position. It was therefore decided to compare the thermodynamic equilibrium ratios for the other related thioaldehyde cyclopentadiene adducts (53), (54)-(56) and (84). The ratio for (56), endo:exo 3:7, had already been reported⁵⁴.



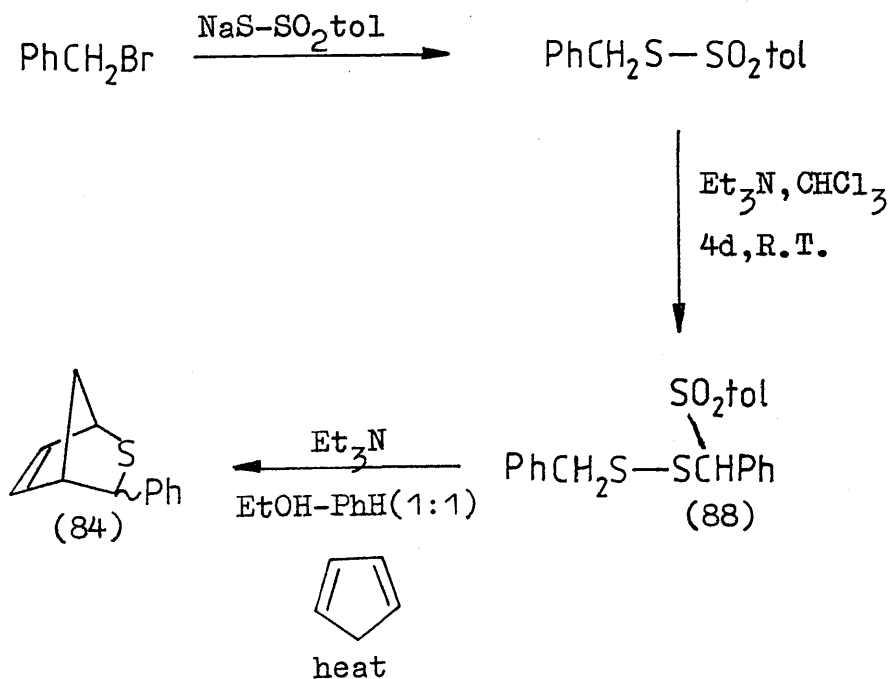
R = 4-BrC ₆ H ₄ CO	(53)
CN	(55)
CO ₂ Et	(56)
C ₆ H ₅	(84)

Although the adducts (52)-(56) could be prepared by the method of Kirby et al.⁵³ from the corresponding Bunte salts, the thiobenzaldehyde adduct (84) could not be prepared by this method, since the electron withdrawing effect of the phenyl group was not sufficient to make the benzylic protons acidic enough to be removed by base. A number of methods have now been reported in the literature for the preparation of (84)⁵⁵⁻⁵⁸. Of these, two were attempted. Krafft and Meinke⁵⁵ reported that (84) could be prepared in good yield by fluorodesilylation of α -silyl disulphides. Thus, following their method, benzyl mercaptan was silylated to give the silyl thiol (85) which was treated with sulphenyl chloride (86) to give the disulphide (87). When this was treated with caesium fluoride, thiobenzaldehyde was generated and trapped in situ by cyclopentadiene under mild conditions (Scheme 49). However, repeatedly the yield of (87) was low. Kirby et al.⁵⁶ generated thiobenzaldehyde by base-induced elimination when the less effective sulphite leaving group had been replaced by the more effective toluene 4-sulphonate (tosylate) group. In practice the reaction was found to proceed via the α -sulphonyl disulphide (88) which upon prolonged treatment with triethylamine underwent fragmentation-elimination to give two equivalents of thiobenzaldehyde. This was trapped to give the cyclopentadiene adducts (84) in

reasonable yield (Scheme 50). A satisfactory yield of the adducts (84) was obtained in this way.



Scheme 49.



tol = 4-MeC₆H₄

Scheme 50.

The endo-exo mixtures of cycloadducts (53)-(56) and (84) formed at room temperature were shown to have kinetically controlled endo:exo ratios, since on heating in refluxing toluene, all the mixtures became richer in the exo component. In each case, heating was continued until there was no further change in the exo:endo ratio. The kinetic and thermodynamic endo:exo ratios, i.e. those before and after equilibration, are shown in Tables II and III. In all cases the endo:exo ratios were determined from ^1H n.m.r. signal integrations.

Table II. Endo:exo ratios of cyclopentadiene thioaldehyde adducts formed at room temperature.

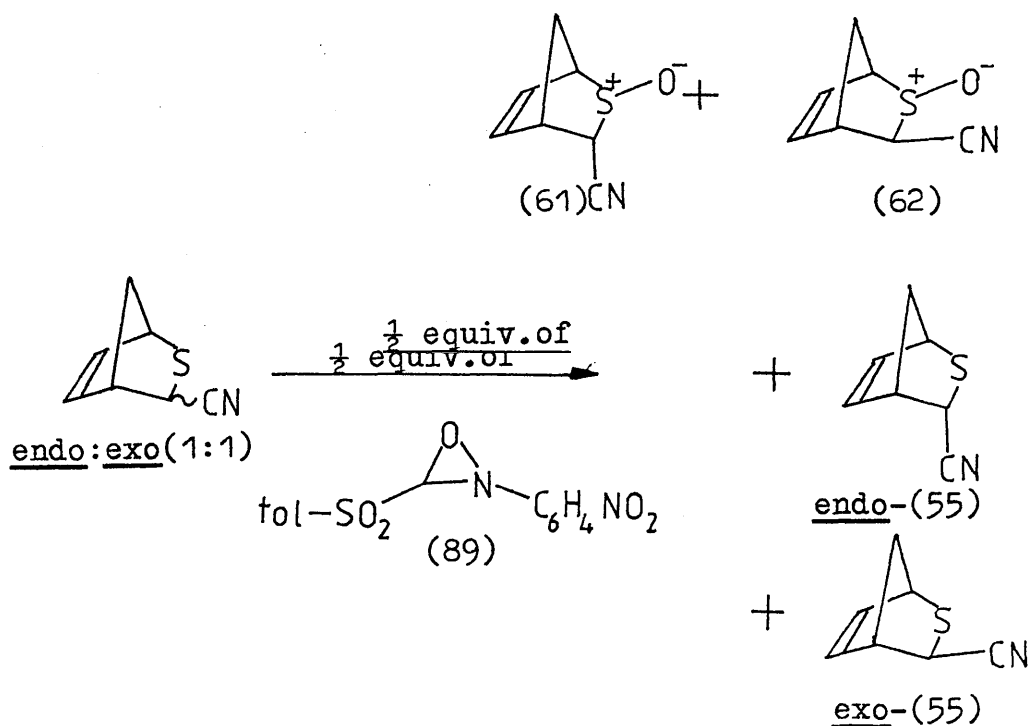
R	<u>endo</u>	<u>exo</u>
CO_2Et (56) ⁵³	7	3
4- $\text{BrC}_6\text{H}_4\text{CO}$ (53) ⁵⁶	8	3
CN (55) ⁵³	2	1
4- $\text{NO}_2\text{C}_6\text{H}_4$ (54) ⁵³	7	1
C_6H_5 (84) ⁵⁶	7	1

Table III. Endo:exo ratios of cyclopentadiene thioaldehyde adducts after equilibration at 111°C.

R	<u>endo</u>	<u>exo</u>	Time at 111°C
CO_2Et (56) ⁵⁴	3	7	5h
4- $\text{BrC}_6\text{H}_4\text{CO}$ (53)	1	5	5h
CN (55)	1	1	9h
4- $\text{NO}_2\text{C}_6\text{H}_4$ (54)	1	1	2h
C_6H_5 (84)	1	1	-

As expected all 'kinetic' mixtures were endo rich on account of significant secondary orbital interactions stabilising the transition states leading to the endo product. The highest endo:exo ratios were found for adducts with the bulkiest 3-substituents, viz endo:exo, 7:1 for $R = C_6H_5$ (84) and $R = 4-NO_2C_6H_4$ (54), whereas the lowest endo:exo ratio was found for the adduct having the smallest 3-substituent, i.e. 2:1 for $R=CN$ (55). Increases in the exo component of mixtures upon heating were observed in the order (53)>(56)>(55). The bulk of substituents also decreases in this order. For both (54) and (84) the high endo preference at 110-120°C is difficult to explain. In these cases there may still be significant secondary orbital interaction stabilising the ground state of the endo isomer. It may have been possible to detect this effect by comparing the u.v. spectra of the endo and exo isomers. However in both cases, since these were not separable, this could not be done. Krafft and Meinke⁵⁵ likewise report a high endo:exo ratio for the mixture (84) obtained at room temperature by the method discussed (Scheme 49). They suggest that, while the endo preference may be a kinetic phenomenon, inspection of models indicates that the endo isomer suffers less steric congestion and may be the more stable isomer. Our equilibration shows that there is in fact little or no difference in relative stability.

Although the endo and exo forms of the cyano sulphides (55) could not be separated, it was observed that, when a slight deficit of oxidant was used, some exo sulphide was left unoxidised, i.e. oxidation appeared to be selective. In order to confirm this, one equivalent of the equilibrated sulphide mixture (endo:exo, 1:1) was oxidised with half an equivalent of the hindered oxidising agent, 3-(toluene-4-sulphonyl)-2-(4-nitrophenyl) oxaziridine⁵⁹ (89). After chromatography however the ¹H n.m.r. spectrum showed that two sulfoxides (61) and, presumably, (62) had been formed in the ratio (61):(62), ca 4:1 (Scheme 51). Likewise the faster running band was a mixture of both the sulphides endo-and exo-(55).

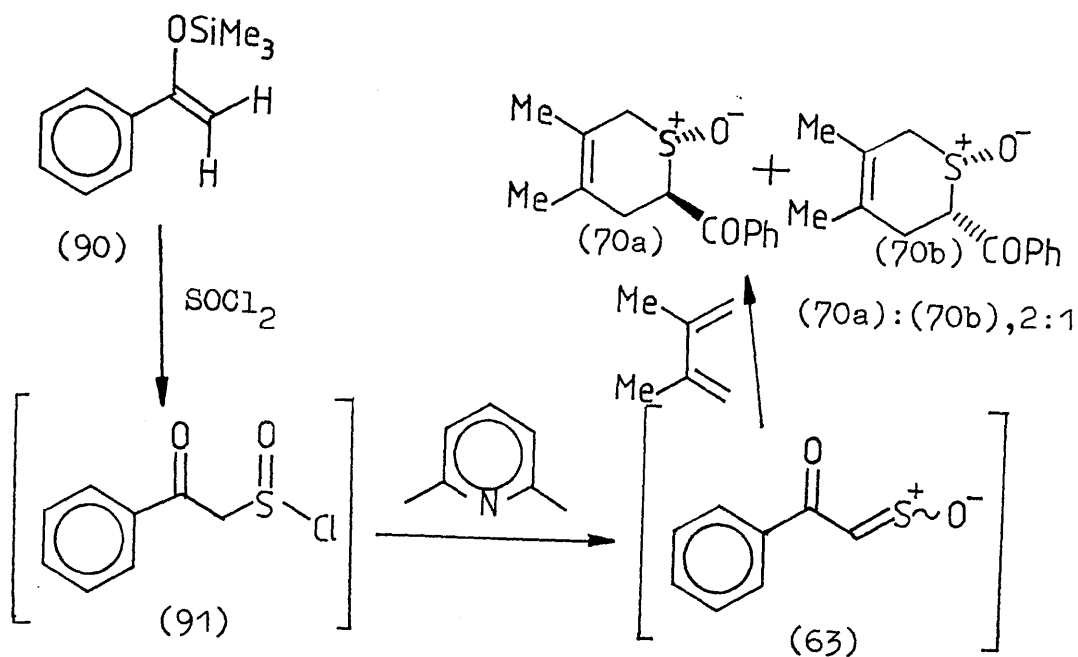


Scheme 51.

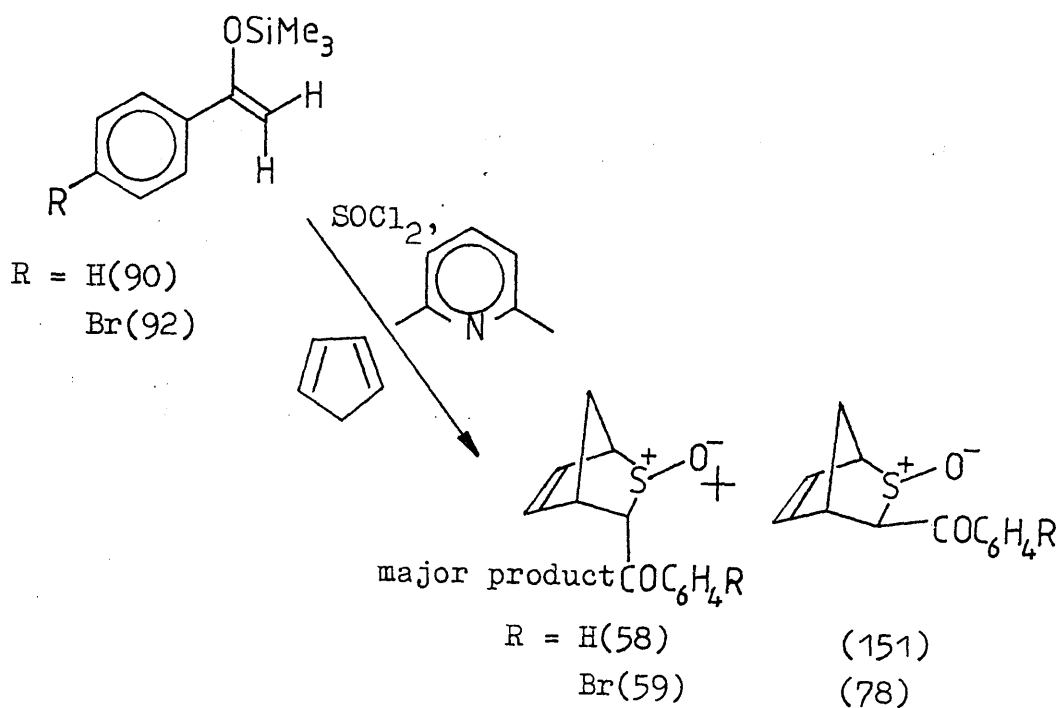
Generation of sulphines by dehydrochlorination of sulphinyl chlorides.

Firstly, an experiment by Zwanenburg et al.⁴¹ was repeated to determine the cis:trans ratio of the sulphine cycloadducts, which had not been reported. Thus the silyl enol ether (90), prepared by the method of House et al.⁶⁰ in 65% yield, was treated in dichloromethane at -78°C with thionyl chloride to form the sulphinyl chloride (91). Addition of 2,6-lutidine then effected elimination of hydrogen chloride and generated the mixture of sulphines (63). These were trapped in situ using 2,3-dimethylbuta-1,3-diene (5 mol equivalents) to give a 1:2, cis:trans mixture of sulphoxides (70)(Scheme 52). However, when the same procedure was repeated, using cyclopentadiene as the diene 'trap' in place of butadiene, (58) was obtained as the major product along with only minor traces of another product, which was later identified as the sulphoxide (151). In the same way, silyl enol ether (92) reacted to give (59) as the major product along with traces of the minor sulphoxide (78) (Scheme 53).

In order to determine whether ethyl thioacetate S-oxide could be generated in a like manner and trapped using cyclopentadiene, the sulphinyl chloride (93) was prepared, as a mixture with acetyl chloride, from ethyl mercaptoacetate by the method of Herrmann and Youn⁶¹ in 87% yield. When the sulphinyl chloride (93) was



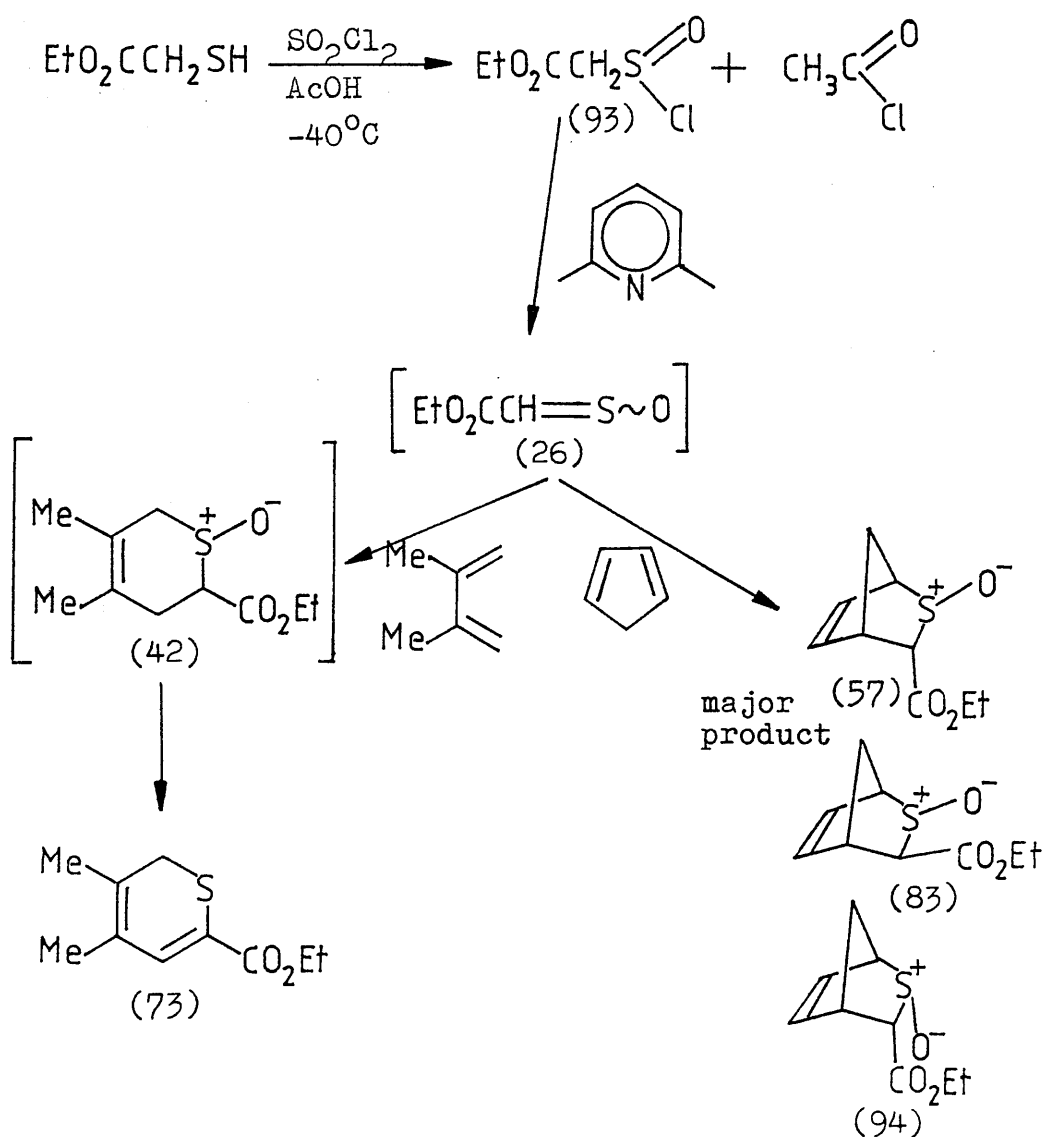
Scheme 52.



Scheme 53.

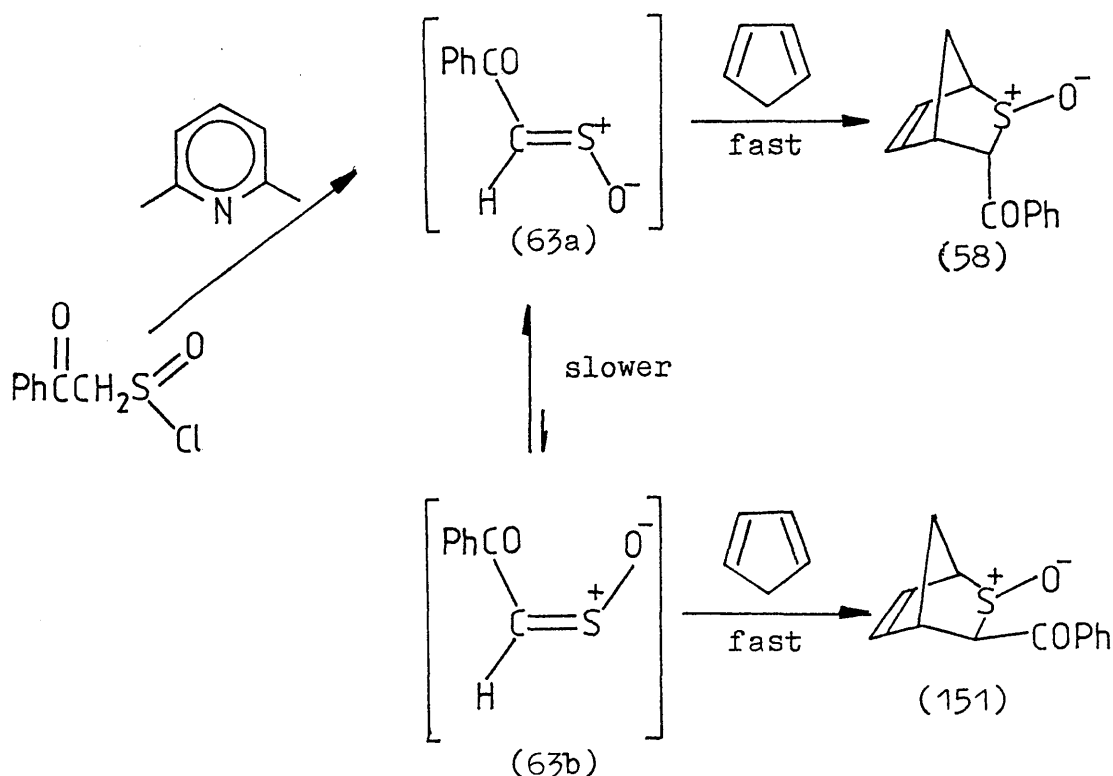
treated with 2,6-lutidine in the presence of cyclopentadiene, (57) was indeed obtained as the major product along with traces of two minor products. These were thought, from their ^1H n.m.r. spectra, to be (83) and (94), although they were present in

quantities too small for the unambiguous assignment of their structures. When (26) reacted with 2,3-dimethylbuta-1,3-diene, in place of cyclopentadiene, the thiapyran (73) was obtained as the major product (Scheme 54), having a ^1H n.m.r. spectrum identical to that of a sample prepared by Lewis⁵² [$\delta(\text{CDCl}_3)$ 1.29 (t, $\underline{\text{J}}7\text{Hz}$, CH_2CH_3), 1.71 and 1.72 (2xs, 4- and 5-Me), 3.20 (m, 6- H_2), 4.24 (q, $\underline{\text{J}}7\text{Hz}$ CH_2CH_3) and 7.07 (s, 3-H)] As discussed earlier, it is again assumed that (73) is formed by a Pummerer rearrangement of the intermediate sulfoxide (42).

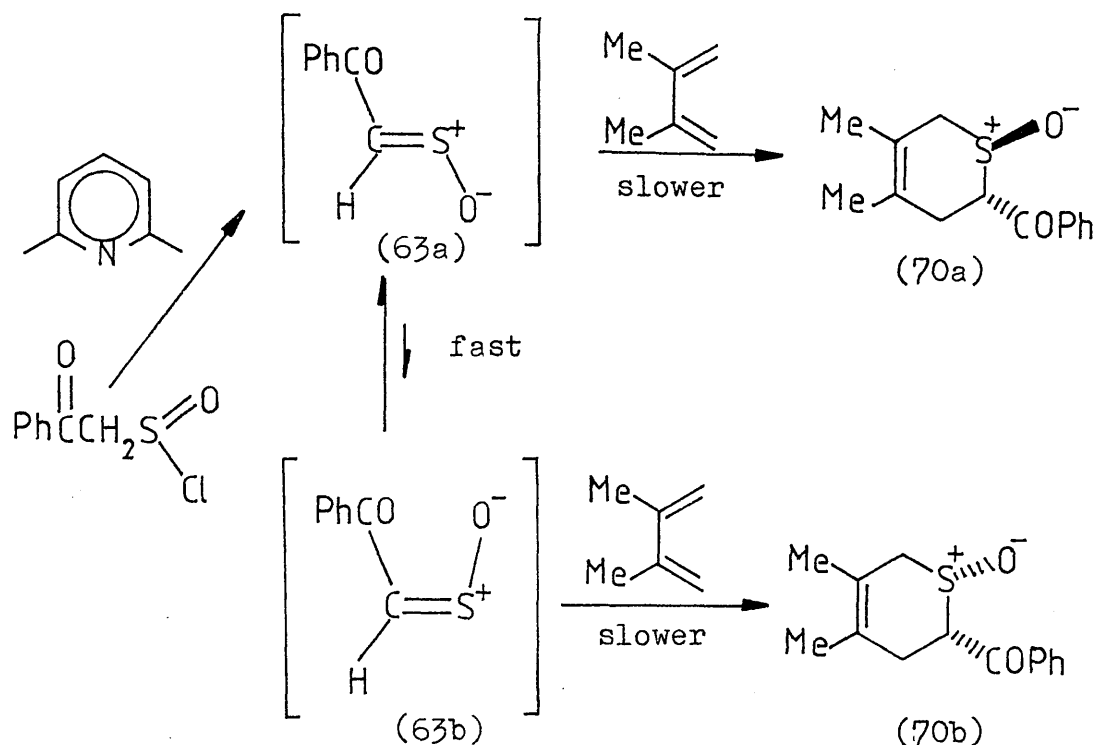


Scheme 54.

The different cis:trans sulphoxide ratio observed for trapping with dimethylbutadiene (Scheme 52) compared with that observed for trapping with cyclopentadiene (Scheme 53) is difficult to explain. The fact that trapping with cyclopentadiene gave mainly the trans sulphoxide (58), accompanied by only minor traces of the cis sulphoxide (151), may indicate that the base induced equilibration of the sulphines (63) was occurring slower than their cycloaddition with cyclopentadiene (Scheme 55). In contrast, the products of cycloaddition (70a) and (70b) with the less reactive dimethylbutadiene may be those of the equilibrated sulphine mixture, richer in the cis sulphine (63b) (Scheme 56). Sauer *et al.*⁶² showed that maleic anhydride reacted much faster with cyclopentadiene than it did with dimethylbutadiene.



Scheme 55.

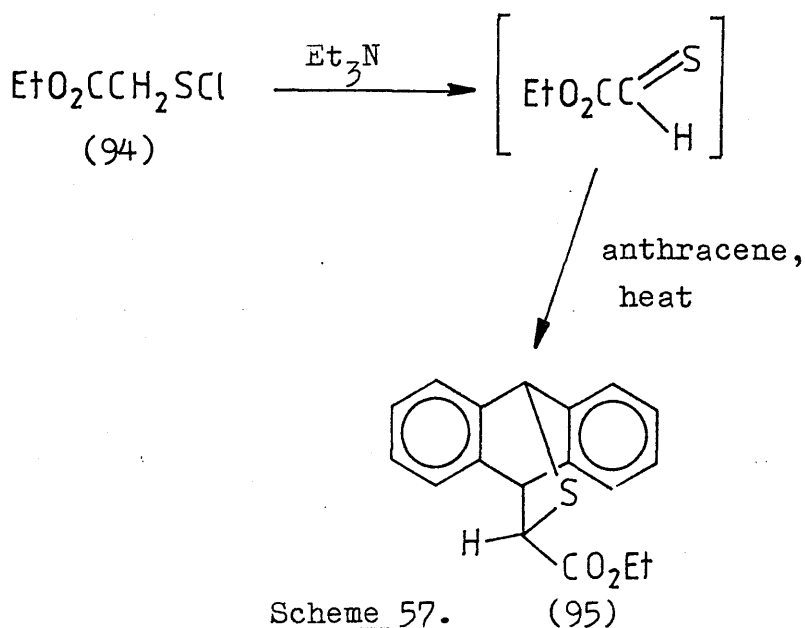


Scheme 56.

Anthracene thioaldehyde adducts and their sulphoxides.

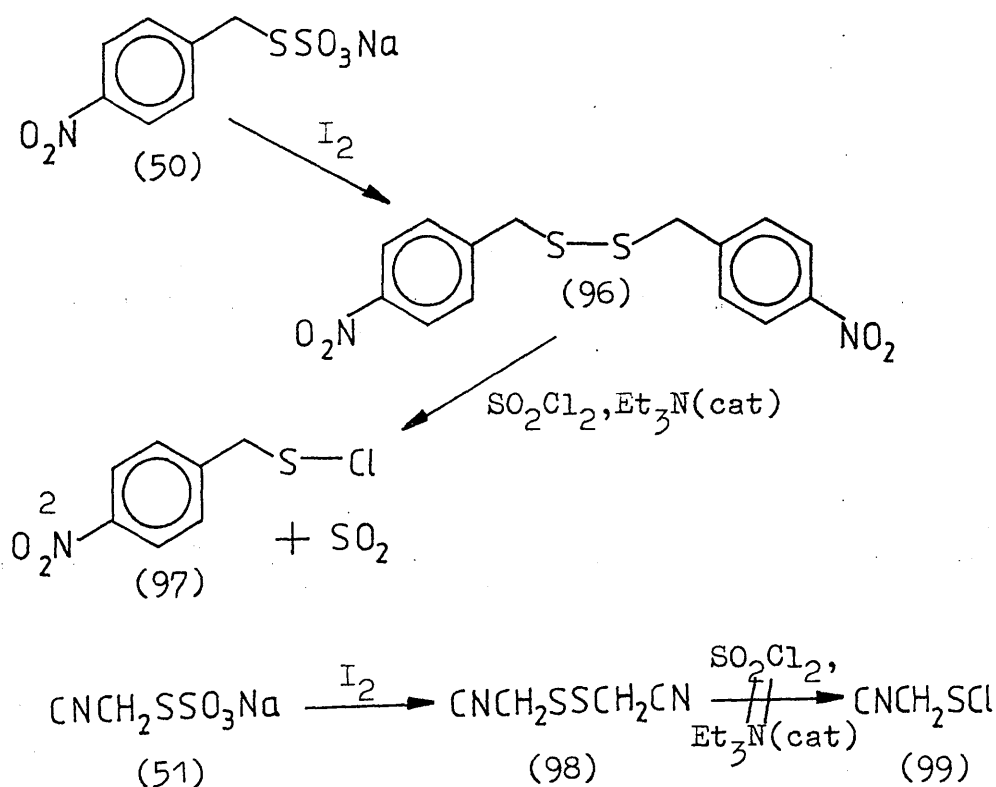
Although initially oxidation of cyclopentadiene thioaldehyde adducts seemed an attractive route to cis and trans sulphoxides and thence sulphines, the approach was found to suffer from one major limitation; namely, that only in one or two cases were the mixtures of exo and endo thioaldehyde adducts readily separable. To avoid this problem therefore, a cyclic diene was chosen which would give only one Diels-Alder adduct. Anthracene was such a 'diene'. No general method was available in the literature however for the preparation of a series of anthracene thioaldehyde adducts corresponding to the cyclopentadiene series prepared by Kirby et al.⁵³. Two methods from the literature were investigated for the preparation of anthracene thioaldehyde adducts.

The first method was that of Kirby et al.⁶³, who prepared the adduct (95) of anthracene with the thioaldehyde ethyl thioacetate, generated in situ from the corresponding sulphenyl chloride (94) (Scheme 57).



For an attempt to extend this method to other anthracene thioaldehyde adducts, it was first necessary to make the sulphenyl chlorides (97) and (99). Sheldrake⁶⁴ had made the former by a modification to the method of Harpp et al.⁶⁵, generating the yellow sulphenyl chloride (97) by base-catalysed cleavage of the corresponding disulphide (96) with sulphuryl chloride at room temperature (Scheme 58). This preparation was successfully repeated. The sulphenyl chloride (99) however could not be generated by this method. The

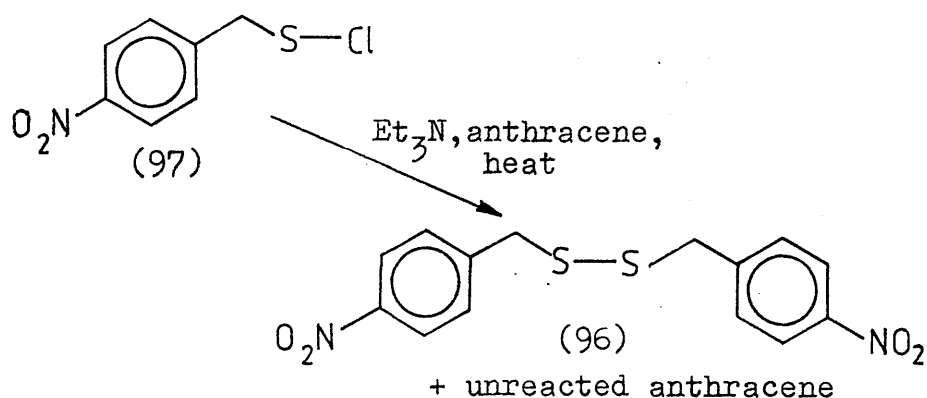
required disulphide (98) was readily obtained from the Bunte salt (51). However, after each attempt at cleavage with sulphuryl chloride, the disulphide (98) was shown by ^1H n.m.r. spectroscopy not to have reacted. Even after prolonged periods of stirring or with slight heating (60°C) formation of a yellow sulphenyl chloride could not be detected.



Scheme 58.

4-Nitrophenylmethanesulphenyl chloride (97) in benzene was added dropwise to an excess of anthracene in refluxing chloroform containing one equivalent of triethylamine. After a further 30 minutes, the mixture was cooled, filtered to remove anthracene,

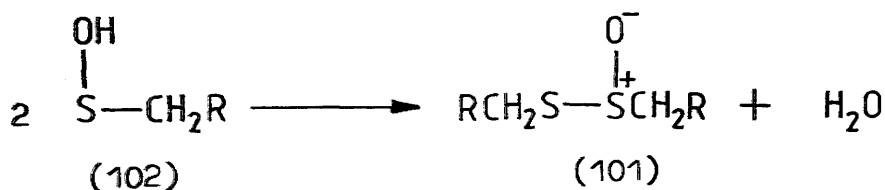
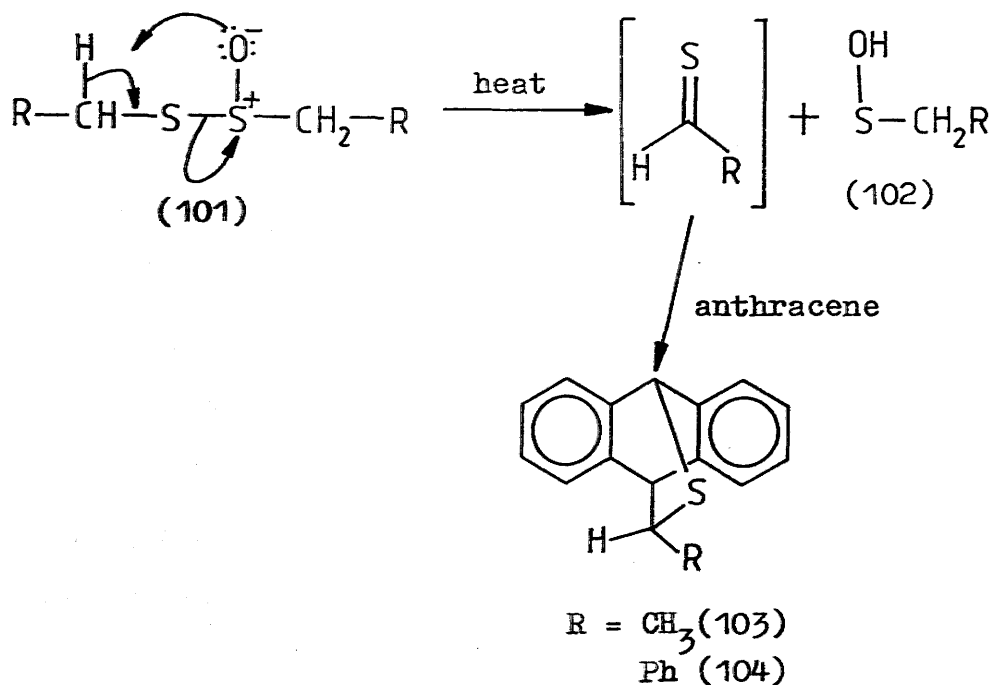
washed with base, dried, and concentrated. However, no traces of the adduct (100) could be detected by ^1H n.m.r. spectroscopy. In several experiments, dibenzyl disulphide (30%), along with unreacted anthracene and unidentified by-products, were isolated from the reaction mixture (Scheme 59). Kirby *et al.*⁶³ prepared the adduct (95) in 37% yield by a similar procedure.



Scheme 59.

The second method was developed by Baldwin and Lopez⁶⁶ for the production of anthracene adducts of thiobenzaldehyde and thioacetaldehyde. They were able to generate thermally these thioaldehydes, along with the related sulphenic acids (102), by [3,3] sigmatropic rearrangement of the corresponding alkyl thiosulphinates (101) (Scheme 60). The thioaldehydes were trapped *in situ* by anthracene to give the cycloadducts (103) and (104). This reaction was first discovered by Block *et al.*⁶⁷, who had succeeded

in trapping the sulphenic acids with acetylenes but had ignored the thioaldehydes. Very good yields of the anthracene adducts (103) and (104) were obtained since the alkyl thiosulphinates (101) were regenerated in situ from the initially formed sulphenic acids (102) (Scheme 60). Adduct (104) was prepared in this way in 98% yield.

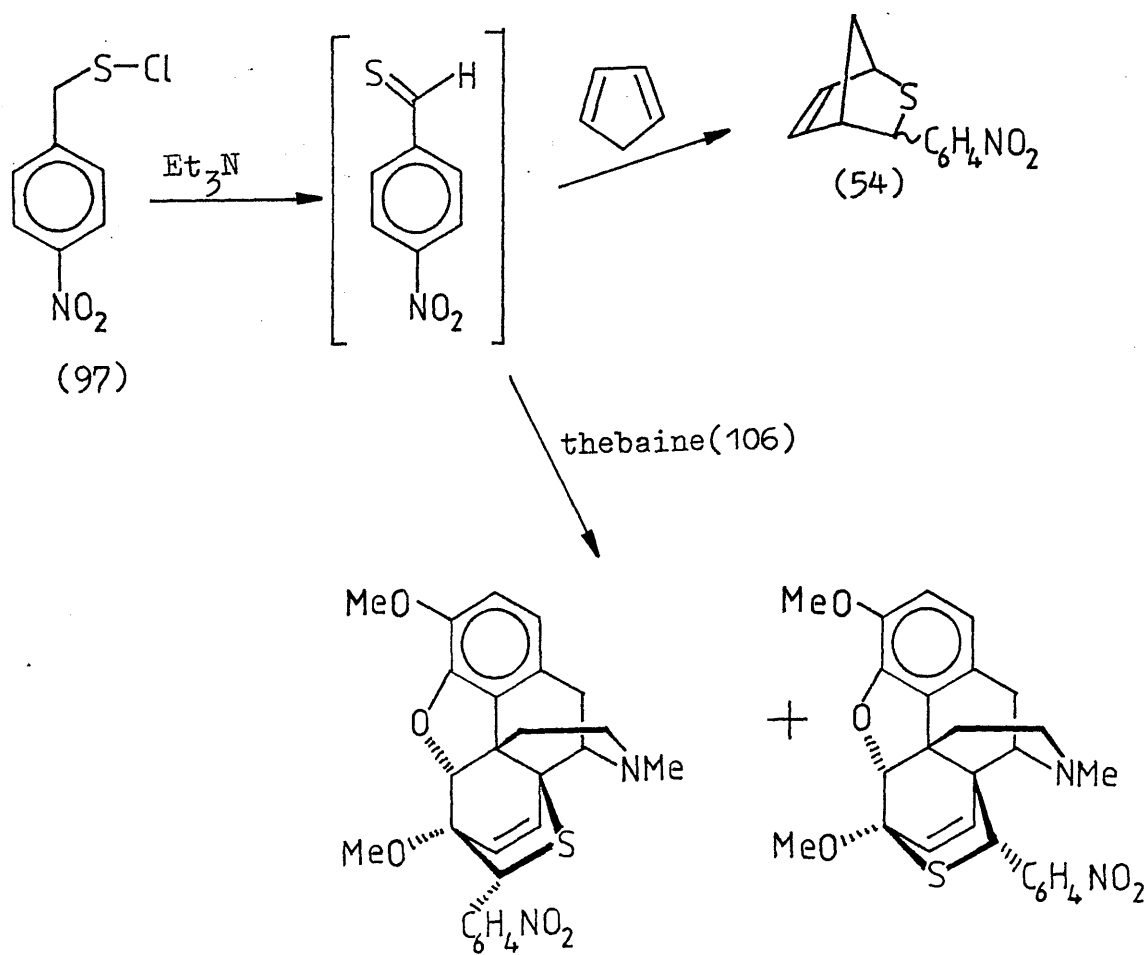
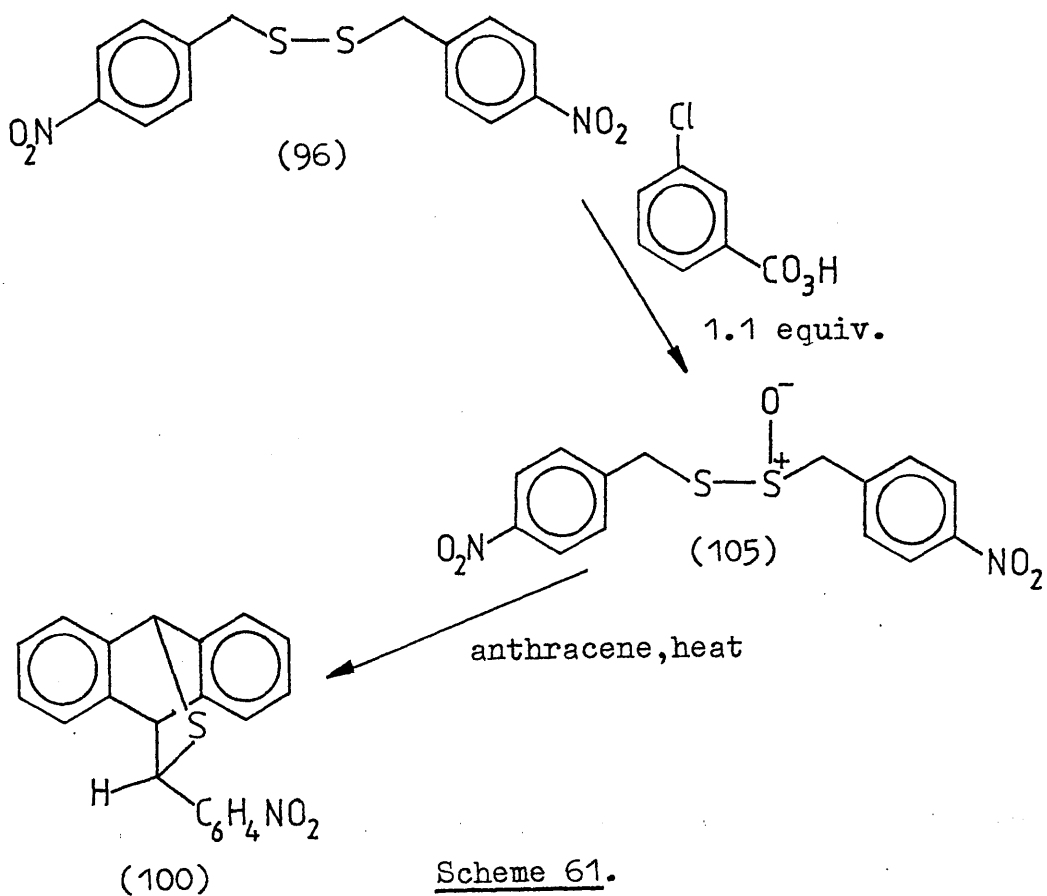


Scheme 60.

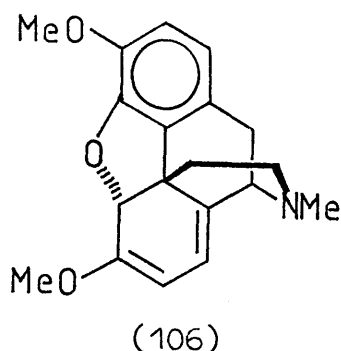
Since 4-nitrothiobenzaldehyde is similar in structure to thiobenzaldehyde, it was expected that this method might succeed, provided that the electron-withdrawing effect of the nitro group did not adversely affect the pericyclic reaction. Thus the dinitro

disulphide (96), prepared as before, was oxidised with 1.1 equivalents of 3-chloroperbenzoic acid to give the alkyl thiosulphinate (105), which was heated in toluene at ca 100°C with ten equivalents of anthracene (Scheme 61). After ca 1h it was shown by ^1H n.m.r. spectroscopy that all the alkyl thiosulphinate had been consumed and that (100) had been formed in 80% yield along with a little dibenzyl disulphide. With a shorter reaction time (0.5h), the yield of (100) was greater (96%). This can be explained if the longer reaction time permitted more of the unstable adduct to dissociate, releasing the reactive thioaldehyde, some of which decomposed before being recaptured. The shorter reaction period must have been closer to the time when all the alkyl thiosulphinate had been consumed, so allowing less time for adduct decomposition. The fact that this method was successful whereas the sulphenyl chloride method failed may be as a result of the higher reaction temperature needed to trap the 4-nitrothiobenzaldehyde by the unreactive anthracene. Sheldrake⁶⁴ however succeeded in generating 4-nitrothiobenzaldehyde from the sulphenyl chloride (97) and trapping it efficiently using thebaine (106) and cyclopentadiene at lower temperatures (Scheme 62).

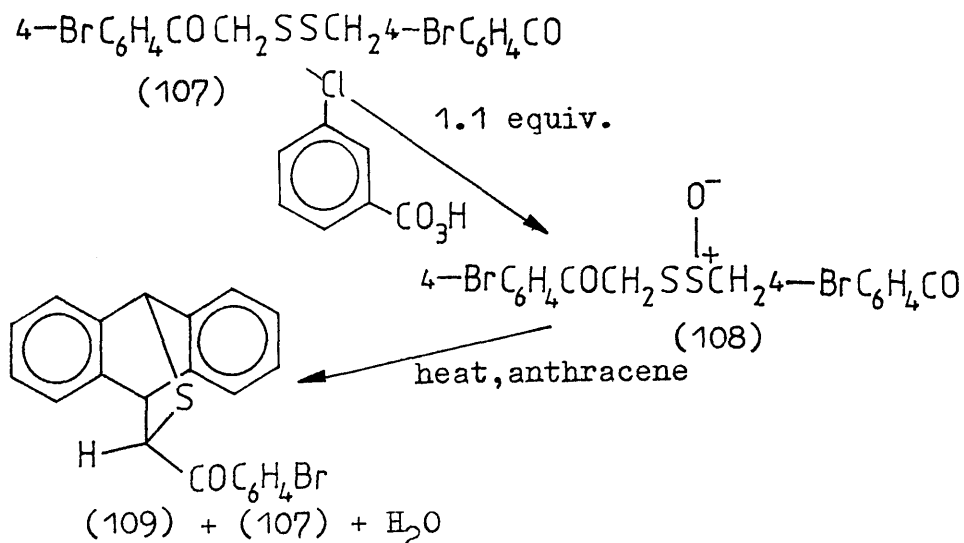
Following the successful preparation of (100), it was decided to prepare the 4-bromobenzoyl derivative (109)



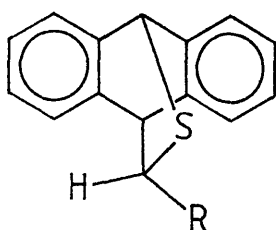
Scheme 62.



in a similar way. Thus, the disulphide (107), prepared by oxidation of the corresponding Bunte salt with iodine, was oxidised by peracid to the alkyl thiosulphinate (108) as before, which was heated in toluene at 100°C for 2h under nitrogen in the presence of ten equivalents of anthracene. The required adduct (109) was obtained in 55% yield along with 18% of disulphide (107) (Scheme 63). Longer or shorter reaction times did not improve the yield. The lower yield in this case is difficult to explain. It may be that the alkyl thiosulphinate (108) is more readily attacked by water, the by-product of this reaction, to give the disulphide (107) and other by-products which were not identified.



Scheme 63.

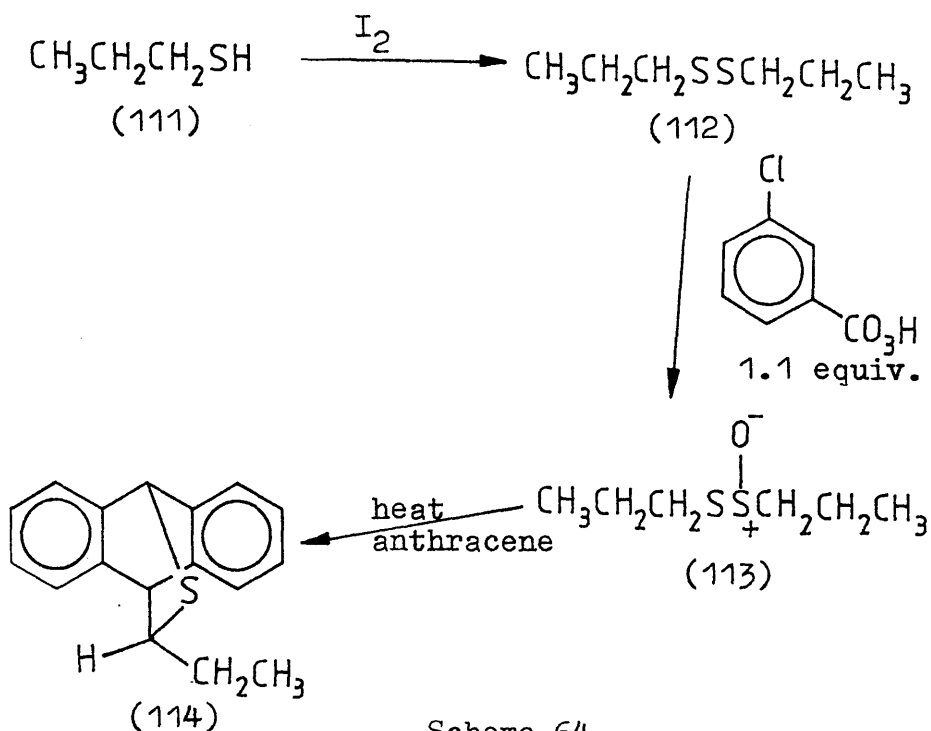


R = CN (110)

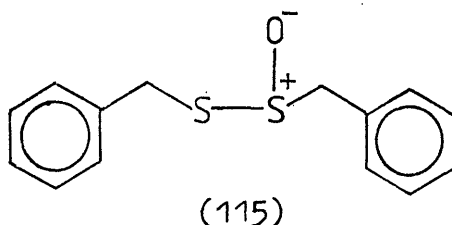
CO₂Et (95)

The procedure was repeated for the preparation of the ethoxycarbonyl (95) and cyano (110) derivatives. However in both cases reaction failed to produce any product, even with higher temperatures (110°C) and longer reaction times. ¹H n.m.r. spectroscopy showed that the alkyl thiosulphinates and anthracene had been recovered unchanged. The ethyl derivative (114) was successfully prepared, however, by a slight variation of the conditions used by Baldwin and Lopez⁶⁶ to prepare the thioacetaldehyde adduct (103). Thus, peracid oxidation of dipropyl disulphide (112), prepared by iodine oxidation of n-propanethiol (111), gave (113) which reacted with ten equivalents of anthracene to give (114) in 80% yield, when the reaction was carried out at 110°C. No cycloadduct was formed at the lower reaction temperature of 100°C (Scheme 64).

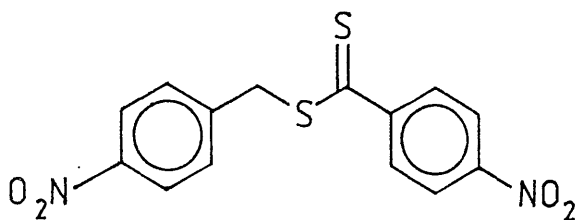
Baldwin and Lopez⁶⁶ also reported that thermolysis of the alkyl thiosulphinic acid (115) in the absence of a diene trap produced the characteristic transient blue



Scheme 64.

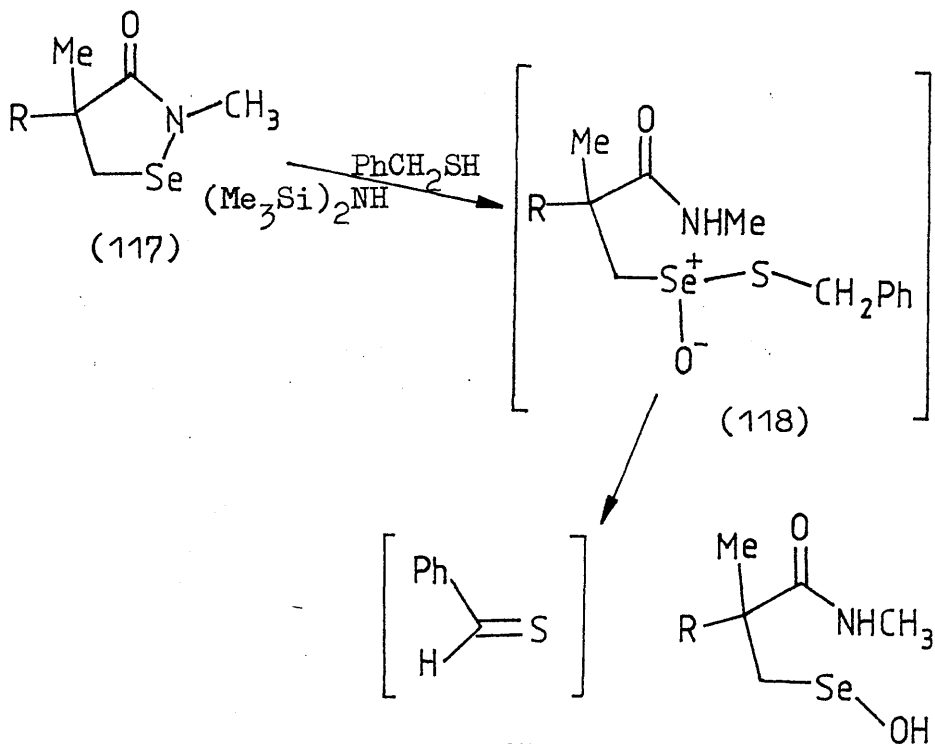


colour of thiobenzaldehyde, and they were able to measure the maximum absorbance at λ 580-590nm. When the alkyl thiosulphinates (105), (108) and (113) were similarly treated, however no transient colour was observed. When the 4-nitrobenzyl derivative (105) was heated a pink colouration was observed which may have been due to the presence of the dithioester (116). Sheldrake⁶⁴ was able to prove, by its synthesis, the presence of this pink species as a by-product in the generation of 4-nitrothiobenzaldehyde.



(116)

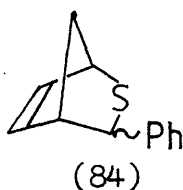
Reich and Jasperse⁶⁸ also observed the characteristic blue colour of thiobenzaldehyde when they treated isoselenazolidine-3-one 1-oxide (117) with benzyl mercaptan under basic conditions. The thioaldehyde was generated at room temperature by rearrangement of the more reactive selenoxosulphide (118) (Scheme 65).



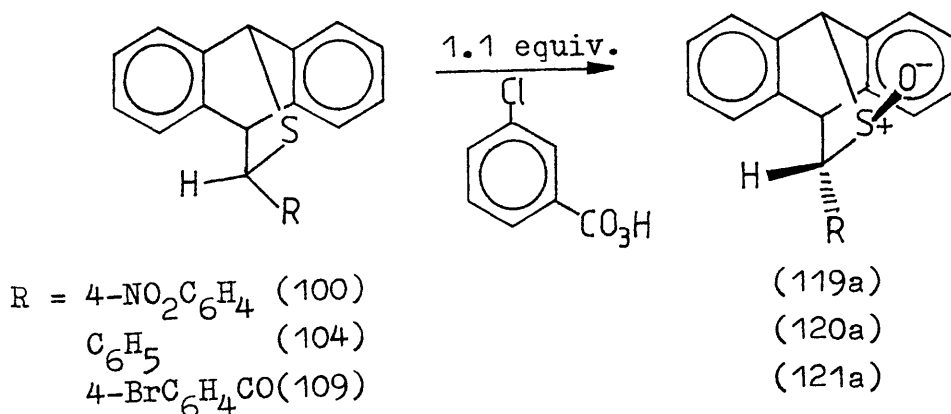
Scheme 65.

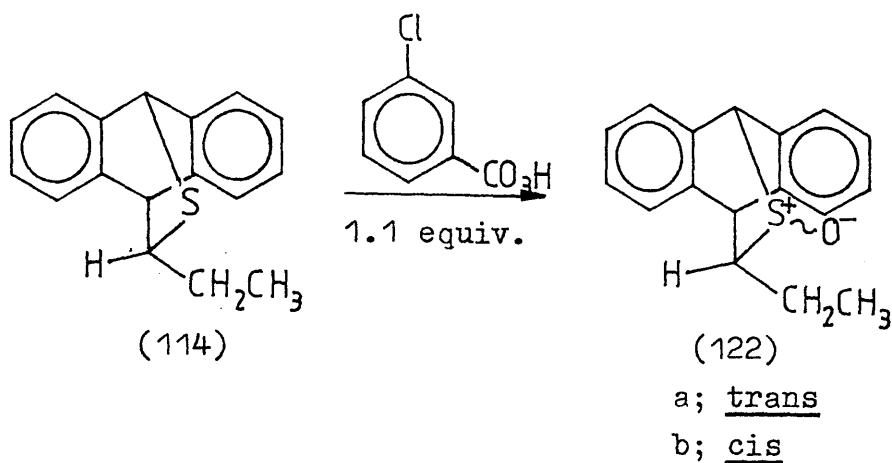
In an attempt to develop this observation into a preparative route to thioaldehydes, we treated benzyl mercaptan with either benzeneseleninic anhydride in dichloromethane or selenium dioxide in

methanol. Both mixtures developed transient blue colours. In both cases however, the same reactants in the presence of cyclopentadiene failed to generate any significant amounts of the adducts (84), probably because the thioaldehyde was being generated in low yield. The method was thus considered to be less attractive than others, particularly the thiotosylate approach used to prepare (84) by Kirby *et al.*⁵⁶, which has been discussed earlier.



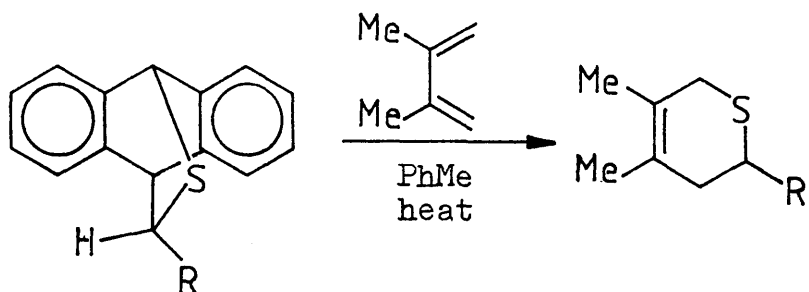
The anthracene adducts (100), (104), (109) and (114) were oxidised using peracid by the usual procedure to give the sulphoxides (119)-(122) (Scheme 66). From the oxidation of (100), (104) and (109) only trans sulphoxides were detected by ¹H n.m.r. spectroscopy. Formation of the cis sulphoxides may be prevented on steric grounds. Oxidation of the ethyl derivative (114) however gave a mixture of cis and trans sulphoxides (122) in the cis:trans ratio 1:2.





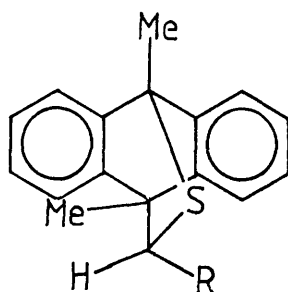
Scheme 66.

When the anthracene adducts (100), (104) and (109) were heated in refluxing toluene under nitrogen along with five equivalents of 2,3-dimethylbuta-1,3-diene, the thioaldehydes were transferred to give the dihydrothiapyrans (76), (123) and (75) in high yields. Reactions were shown to be complete after the times indicated in brackets (Scheme 67). For the propanethial adduct (114) there was no transfer in refluxing toluene after 48h. Baldwin and Lopez⁶⁶ reported that the ethanethial adduct (103) was highly resistant to thermolysis. They found however that the corresponding 9,10-dimethylantracene adduct (124) was more labile to heat, presumably since the retro-Diels-Alder reaction eliminates the steric interaction between the thioacetaldehyde methyl group and the anthracene methyl group, not present in (103). Kirby et al.⁶³, similarly observed that the dimethyl derivative (125) released ethyl thioacetate more easily than did the parent anthracene adduct (95).



R = 4-NO ₂ C ₆ H ₄	(100), (1h)	(76)
C ₆ H ₅	(104), (15mins)	(123)
4-BrC ₆ H ₄ CO	(109), (2h)	(75)
CH ₂ CH ₃	(114), (no transfer)	

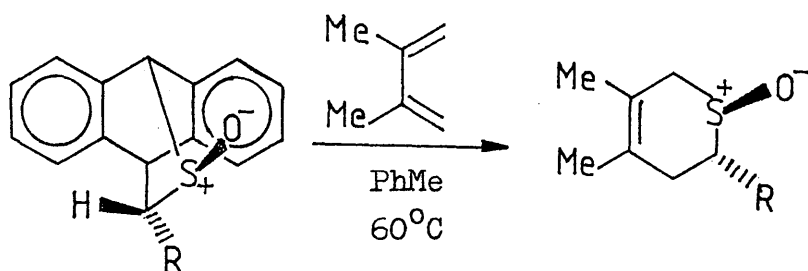
Scheme 67.



R = CH ₃	(124)
CO ₂ Et	(125)

Thermal 'transfer' of thioaldehydes and sulphines from anthracene to dimethylbutadiene.

In all cases, when the trans anthracene sulphine adducts (119a)-(121a) were heated with 2,3-dimethylbuta-1,3-diene (5 mol equiv.) in toluene at 60°C, ¹H n.m.r. spectroscopy showed that 'transfer' of the corresponding sulphines had occurred with complete retention of stereochemistry (see later) to give the trans-sulphoxides (68a), (45a) and (67a) exclusively in 68-82% yield (Scheme 68). As discussed earlier, the structures of the product sulphoxides were verified by

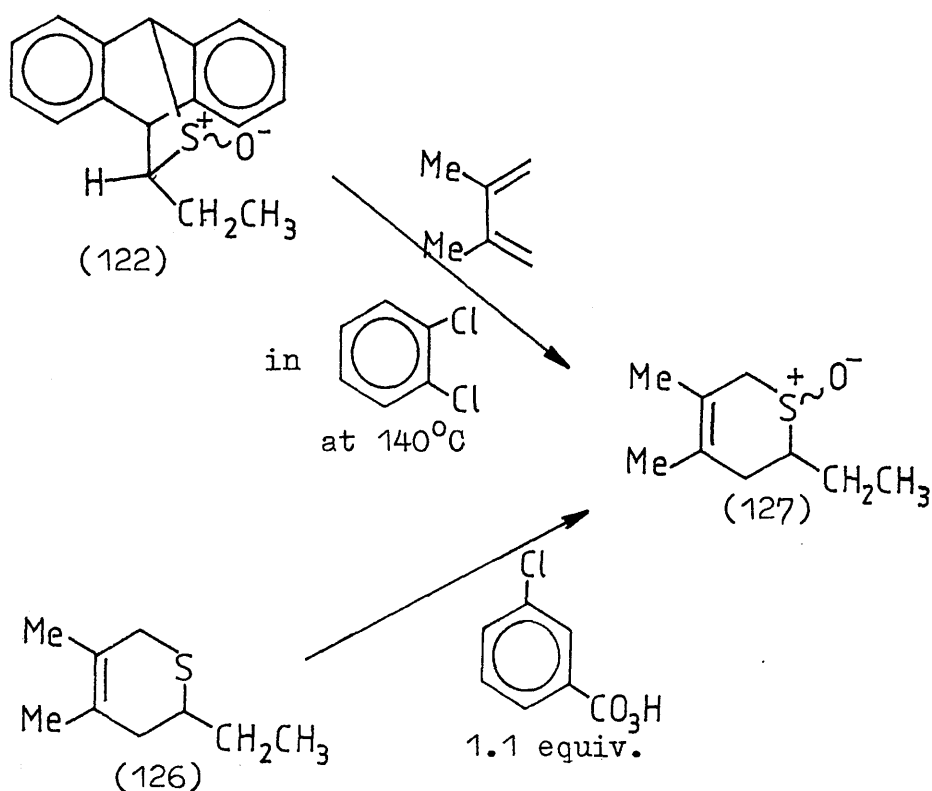


			<u>Reaction times/h</u>
R = 4-NO ₂ C ₆ H ₄	(119a)	(68a) ^a	1-2h
C ₆ H ₅	(120a)	(45a) ^b	2-3h
4-BrC ₆ H ₄ CO	(121a)	(67a) ^a	4-5h

Scheme 68.

their synthesis^a and by comparison with ¹H n.m.r. data for the literature standard^b.

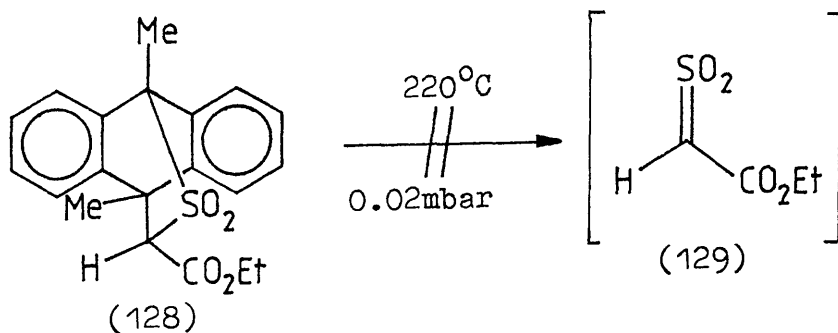
When the cis:trans (1:2) sulfoxide mixture of propanethial adducts (122) was heated in refluxing toluene for 48h with dimethylbutadiene (5 equiv.) no apparent change occurred with the ¹H n.m.r. spectrum indicating that both sulfoxides were still present, although the mixture became somewhat dark in colour. After being heated in o-dichlorobenzene at 140°C, however, the ¹H n.m.r. spectrum of the same mixture indicated that both sulfoxides had reacted. The product mixture was complex; however, chromatography gave a low yield (22%) of the sulfoxides (127), the ¹H n.m.r. signals for which agreed fairly closely with those of a mixture synthesised by oxidation of (126), prepared by the method of Baldwin and Lopez⁶⁶ (Scheme 69). The cis:trans ratio of the product sulfoxides (127) could not be determined by n.m.r. spectroscopy although both were presumed to be present.



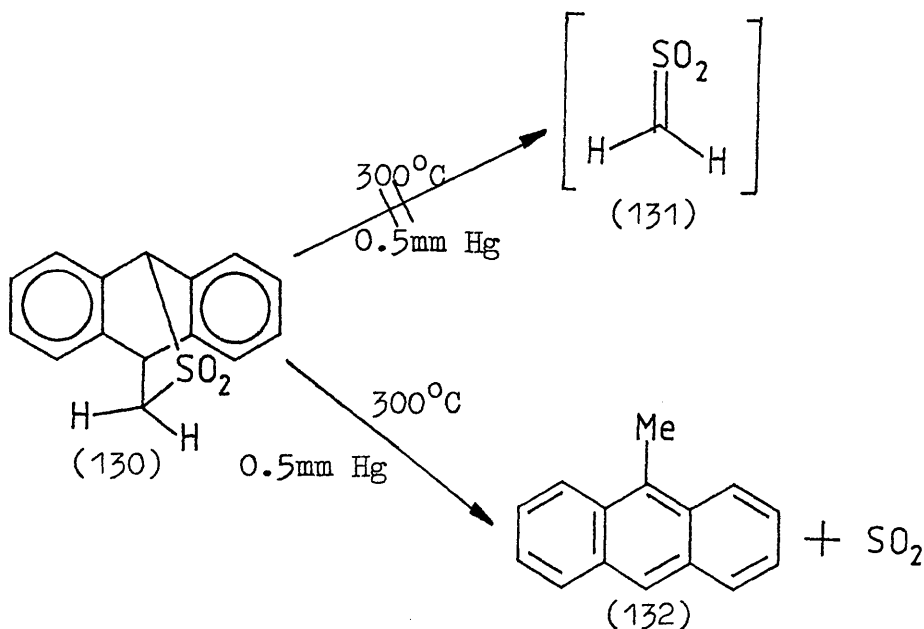
Scheme 69.

These experiments show that the rate of release of both thioaldehydes and sulphines from their anthracene adducts is markedly dependent upon the nature of the α substituent. For both thioaldehydes and sulphines, the reactivity was of the order $4-NO_2C_6H_4 > C_6H_5 > 4-BrC_6H_4CO > CO_2Et \gg CH_2CH_3$. Frontier molecular orbital (f.m.o.) considerations predict that the energy of the lowest unoccupied molecular orbitals (LUMOs) is lowered by electron withdrawing substituents, so that the energy of the transition states in the Diels-Alder reactions is reduced. Indeed such substituents are known normally

to increase reaction rates. The retro-Diels-Alder reactions will be affected similarly providing that the substituents do not affect the relative energies of the reactant and product ground states. These results also show that the size of the substituents is particularly important with sulphines having more bulkier substituents being released more readily, presumably to relieve greater strain. As found by Lewis⁵², the experiments also showed that sulphines were released at lower temperatures than thioaldehydes. In contrast Lockheed⁶⁹ found that the cycloadduct sulphine (128) did not dissociate to release the sulphene (129); instead it was recovered unchanged from a Kugelrohr tube at 220°C (0.02mbar) after 30 min (Scheme 70). Similarly, Hales *et al.*⁷⁰ found that the sulphone (130) failed to release the sulphene (131) upon thermolysis in a sealed tube, evacuated to 0.5mm Hg, at 300°C. Instead, the methyl anthracene (132) was obtained by extrusion of sulphur dioxide (Scheme 71).



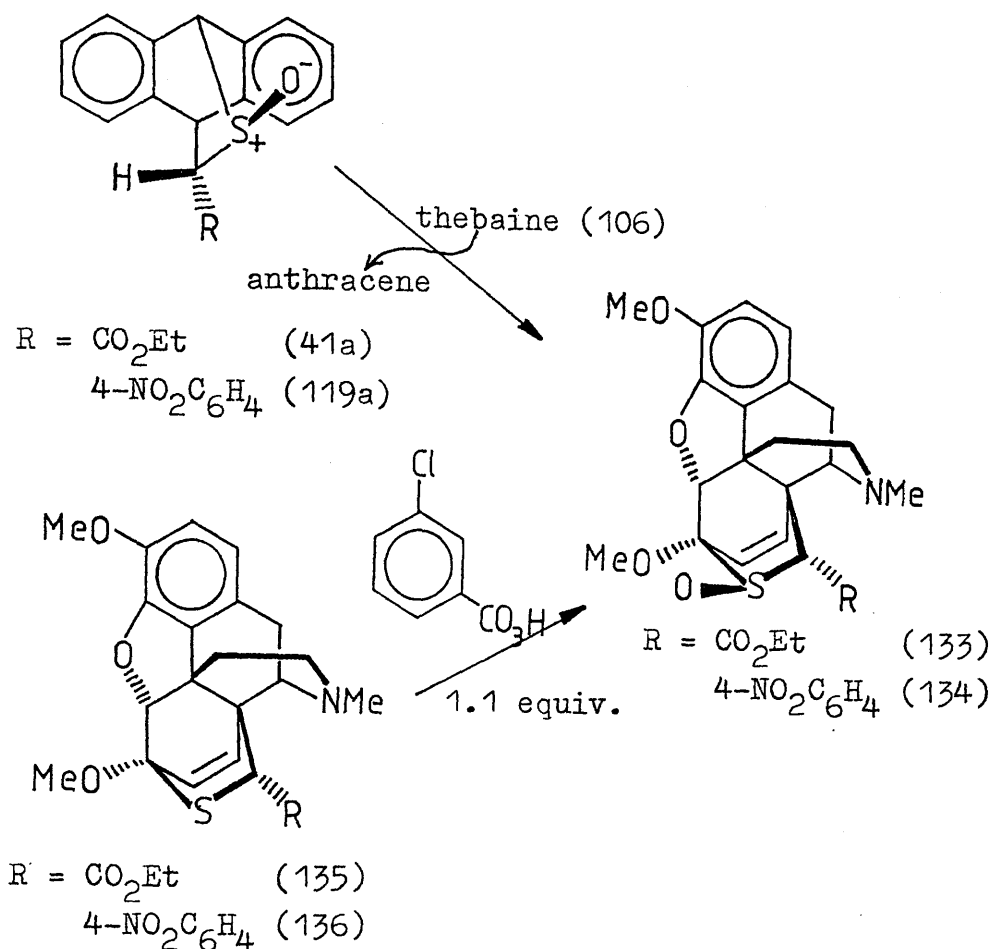
Scheme 70.



Scheme 71.

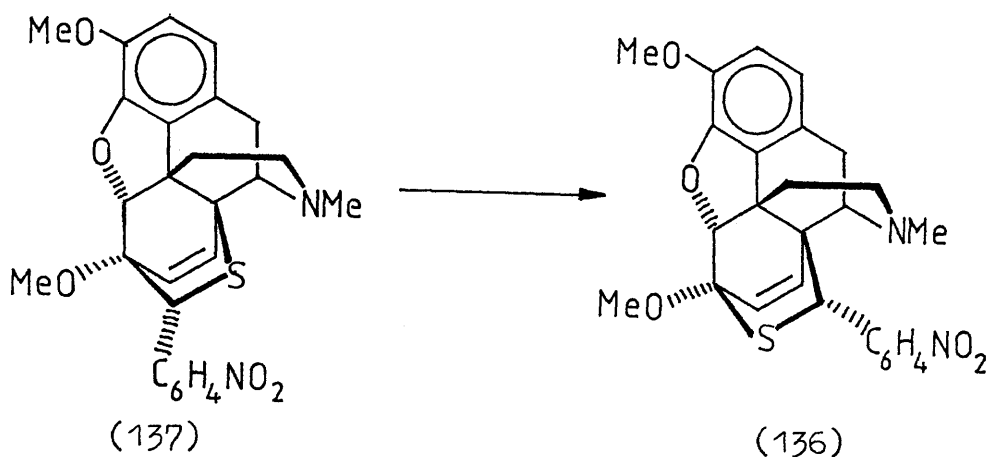
Thermal 'transfer' of sulphines from anthracene to thebaine.

Kirby et al.³⁹ showed that when the sulfoxide (41a) was heated with one equivalent of thebaine (106) in benzene at 60°C , it formed the thebaine adduct (133) as the sole identified product, apart from anthracene. They also showed that (133) was the sole sulfoxide formed when the adduct (135) of thebaine and ethyl thioacetate was oxidised using 1.1 equivalents of peracid. We found, similarly, that when (119a) was heated in benzene at 60°C with thebaine it formed (134). The structure (134) was likewise successfully confirmed by oxidation of the precursor (136); again, only one sulfoxide was formed, (Scheme 72). Determination of the stereochemistry of (134) will be discussed later.



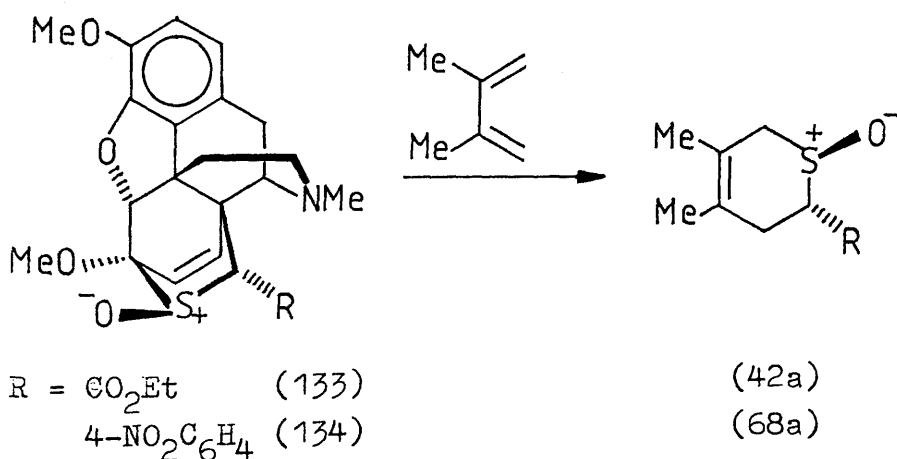
Scheme 72.

Sheldrake⁶⁴ obtained the cycloadducts (136) and (137) as a 1:1 mixture by treatment of the Bunte-salt precursor (50) with triethylamine in the presence of calcium chloride dihydrate and 1.1 mol equivalent of thebaine for 18h at room temperature. This author found that with a reaction time of 5d instead of 18h, (136) was generated exclusively in reasonable yield (Scheme 73). Thus, the thermal equilibration of these adducts apparently proceeds, slowly, even at room temperature.



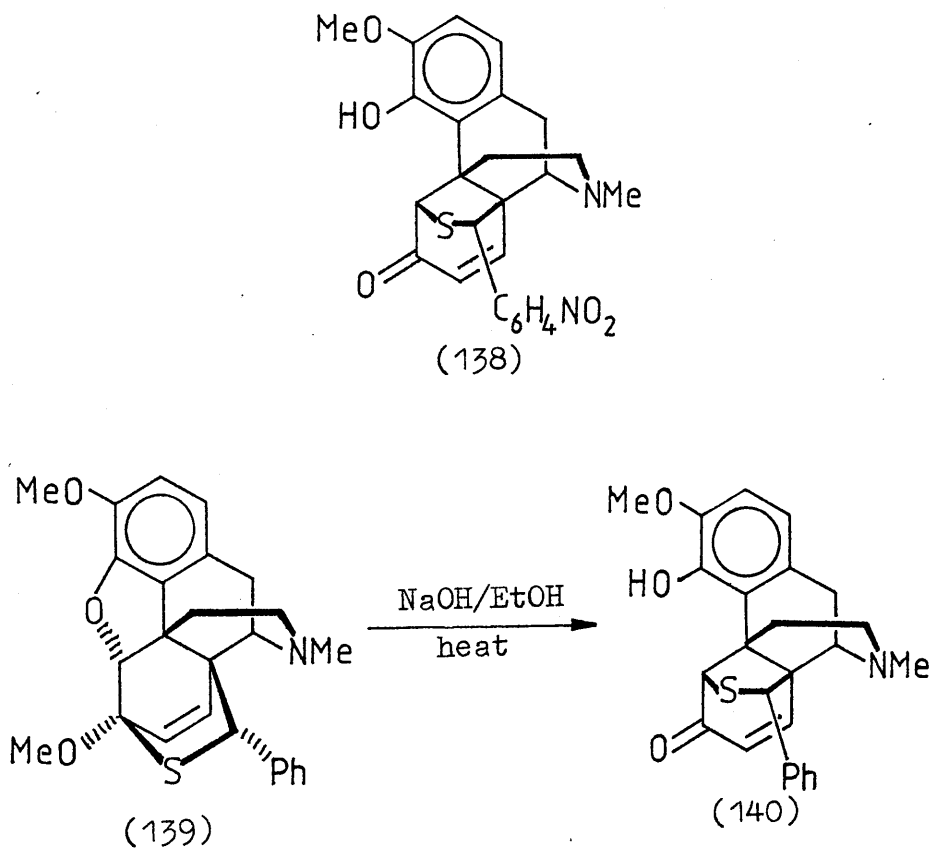
Scheme 73.

Kirby et al.³⁹ were further able to show that the sulphoxide (133), when heated in benzene at 80°C with 2,3-dimethylbuta-1,3-diene (5 equiv.), reacted completely to give the trans sulphoxide (42a) with complete retention of stereochemistry. We found that, when (134) was similarly heated in benzene at 70°C it was recovered unchanged. However, in benzene at 100°C (sealed tube), it likewise reacted to give (68a) in 81% yield (Scheme 74).



Scheme 74.

During the oxidation of the nitrophenyl adduct (136), traces of a by-product were isolated. The ^1H n.m.r. spectrum indicated that this had the morphinan skeleton, but only one methoxy peak, at $\delta 3.82$, was observed. The i.r. spectrum indicated the presence of an $\alpha\beta$ -unsaturated ketone ($\nu_{\text{max}} 1,685\text{cm}^{-1}$) and the mass spectrum gave the parent ion peak at m/z 464. Thus, it seems likely that the by-product $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_5\text{S}$, has the structure (138) shown below. McDougall⁷¹ found that (140) was formed from (139) by treatment with hot ethanolic sodium hydroxide (Scheme 75).



Scheme 75.

Sulphoxide stereochemistry.

Determination of the stereochemistry of cyclopentadiene cycloadduct sulphoxides.

The stereochemistry of the cyclopentadiene sulphine adducts (58)-(61) was determined from their ^1H n.m.r. spectra (Table IV). The trans stereochemistry of the ethyl ester sulphoxide (57) had been proved unambiguously by x-ray analysis³⁹. In its ^1H n.m.r. spectrum, the signal for the 3-H synperiplanar to the sulphoxide oxygen, was shifted upfield by about 1 p.p.m. with respect to the corresponding signal in the sulphide, thus showing a strong shielding effect due to the sulphoxide group. Likewise, a similar shift was observed for sulphoxides (58)-(61). Thus, the sulphoxides (58)-(61) must have the same relative stereochemistry as (57). In contrast, the shifts for the 3-H protons of (78) and (83), anti to the sulphoxide oxygen, relative to those of the corresponding exo sulphides were smaller and in the opposite direction (Table V).

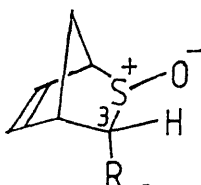


Table IV. ^1H chemical shifts [$\delta(\text{CDCl}_3)$] for endo cyclopentadiene adducts and their trans sulphoxides.

R	3-H(S)		3-H(SO)		$\Delta\delta(\text{S} \rightarrow \text{SO})$
CO_2Et	<u>endo</u> -(56)	4.42 ⁵³	(57)	3.32 ³⁹	-1.10
COPh	<u>endo</u> -(52)	5.12 ⁵³	(58)	4.23	-0.89
$4\text{-BrC}_6\text{H}_4\text{CO}$	<u>endo</u> -(53)	5.01 ⁶¹	(59)	4.25	-0.76
$4\text{-NO}_2\text{C}_6\text{H}_4$	<u>endo</u> -(54)	4.96 ⁵³	(60)	3.91	-1.05
CN	<u>endo</u> -(55)	4.32 ⁵³	(61)	3.11	-1.21

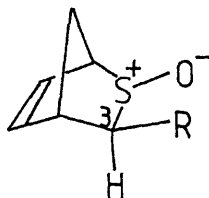
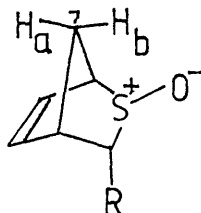


Table V. ^1H chemical shifts $[\delta(\text{CDCl}_3)]$ for exo cyclopentadiene adducts and their cis sulphoxides.

R	3-H(S)		3-H(SO)		$\Delta\delta(\text{S} \rightarrow \text{SO})$
CO_2Et	<u>exo</u> -(56)	3.30	(83)	3.56	+0.26
$4\text{-BrC}_6\text{H}_4\text{CO}$	<u>exo</u> -(53)	3.96	(78)	4.36	+0.40

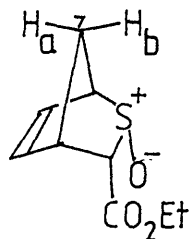
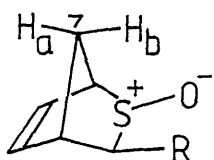
The relative positions of the 7- H_2 proton signals for the cyclopentadiene adduct sulphoxides (57)-(61), (78) and (83), both shifted downfield from their positions in the sulphides by the inductive effect of the positive sulphur, provides further evidence of the proposed stereochemistries (Tables VI and VII). For the sulphoxides (57)-(61), assigned the trans stereochemistry, and (78) and (83), assigned the cis stereochemistry, all of which have an exo oxygen atom, the 7-H chemical shift differences were found to be reasonably consistent. Apparently H_b is selectively deshielded by the sulphoxide oxygen. In contrast, for the cis sulphoxide (94) prepared by Lewis⁵², having an endo oxygen, the 7- H_2 proton signals were found to shift by the same amount, $\Delta\delta(\text{S} \rightarrow \text{SO}) = +0.69$, as expected for an inductive effect of the positive sulphur [see $\Delta\delta(\text{S} \rightarrow \text{SO})$ for H_a in Table VI]

Table VI. ^1H chemical shifts [$\delta(\text{CDCl}_3)$] for endo cyclopentadiene adducts and their trans sulphoxides.



R	7-H(S)		7-H(SO)		$\Delta\delta(\text{S} \rightarrow \text{SO})$		$\Delta\delta(a \rightarrow b)$
				a b	a b		
CO_2Et	<u>endo</u> -(56)	1.66	(57)	2.30 2.56	+0.64 +0.90		+0.26
COPh	<u>endo</u> -(52)	1.68	(58)	2.30 2.67	+0.62 +0.99		+0.37
$4\text{-BrC}_6\text{H}_4\text{CO}$	<u>endo</u> -(53)	1.72	(59)	2.37 2.73	+0.65 +1.01		+0.36
$4\text{-NO}_2\text{C}_6\text{H}_4$	<u>endo</u> -(54)	1.77	(60)	2.48 2.86	+0.71 +1.09		+0.38
CN	<u>endo</u> -(55)	1.88	(61)	2.45 2.79	+0.57 +0.91		+0.34

Table VII. ^1H chemical shifts [$\delta(\text{CDCl}_3)$] for exo cyclopentadiene adducts and an endo cyclopentadiene adduct and their cis sulphoxides.

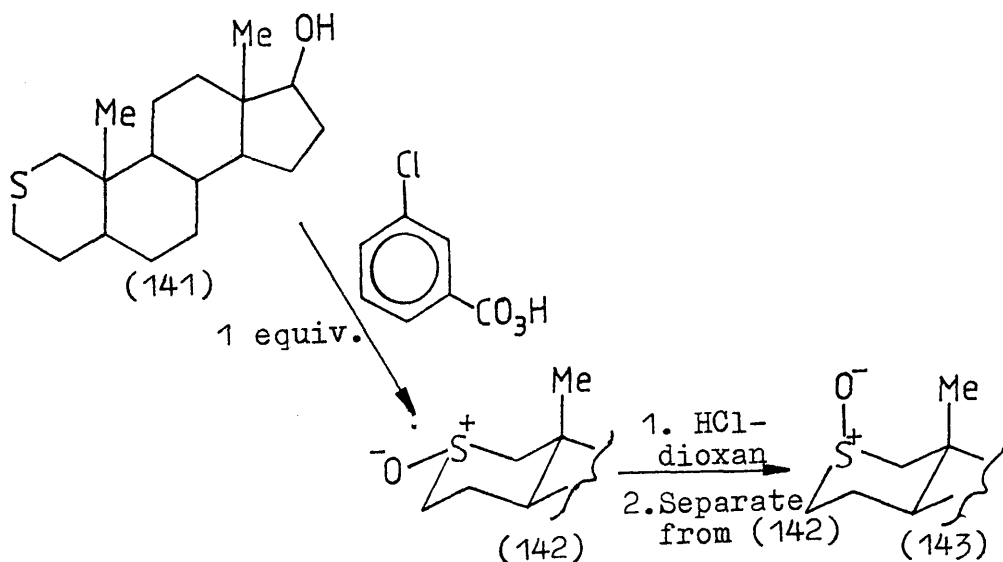


R	7-H(S)		7-H(SO)		$\Delta\delta(\text{S} \rightarrow \text{SO})$		$\Delta\delta(a \rightarrow b)$
		a b		a b	a b		
* CO_2Et	<u>exo</u> -(56)	1.68 1.91	(83)	2.28 2.86	+0.60 +0.95		+0.58
* $4\text{-BrC}_6\text{H}_4\text{CO}$	<u>exo</u> -(53)	1.73 2.00	(78)	2.38 2.97	+0.65 +0.97		+0.59
CO_2Et	<u>endo</u> -(56)	1.66	(94)	2.35	+0.69		0

*In these 2 derivatives, signals for 7- H_a and 7- H_b in the sulphides have different chemical shifts. Presumably 7- H_b in each compound is deshielded by the

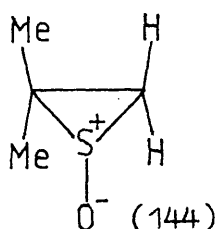
exo group R. With these assignments, the differential shifts upon sulfoxide formation, $\Delta\delta = +0.35$ for (83) and $+0.32$ for (78), agree well with those for the endo derivatives, $\Delta\delta(a \rightarrow b)$ in Table VI.

The following literature reports on the chemical shift effects in sulfoxides support the foregoing assignments. Dodson *et al.*⁷² reported chemical shifts for the steroid (141), the derived sulfoxide (142), and the epimer (143) (Scheme 76). In the α -sulfoxide (142), the protons of the β -methyl group, anti to the sulfoxide oxygen, were slightly shielded relative to those in the sulphide (141), $\delta 1.07 \rightarrow 0.98$ ($\Delta\delta = -0.09$), whereas in the β -sulfoxide (143) the protons of the β -methyl group syn to the sulfoxide oxygen, were deshielded, $\delta 1.07 \rightarrow 1.33$ ($\Delta\delta = +0.25$). The latter effect is similar to that observed in the trans sulfoxides (57)-(61) (Table VI).



Scheme 76.

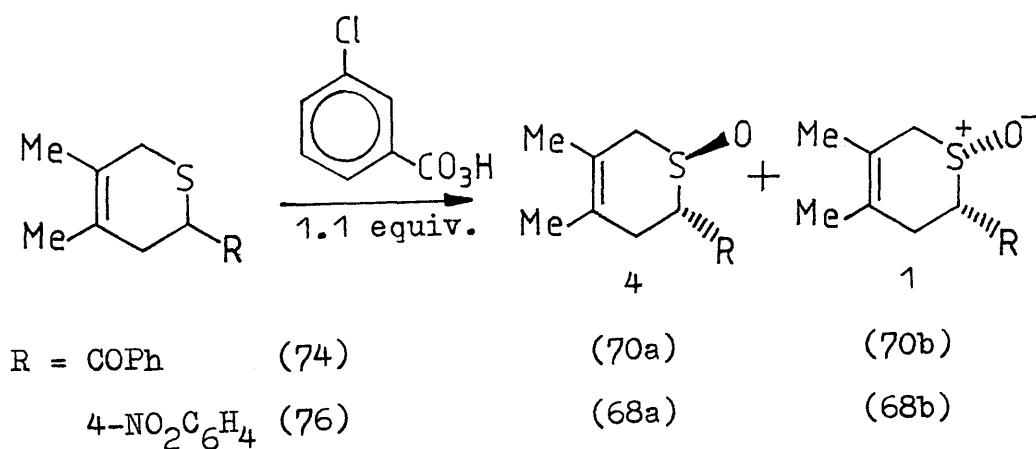
Likewise Kando and Negishi⁷³ found that, for the 3 membered ring sulfoxide (144), the protons of the methyl group syn to the sulfoxide oxygen were deshielded relative to those in the sulphide (144), whereas, those of the methyl group anti were slightly shielded. Thus, when the episulphide was oxidised to the sulfoxide (144), the signals for the protons of the syn methyl group were shifted from $\delta 1.59 \rightarrow 1.77$ ($\Delta\delta = +0.18$), whereas the signals for the protons of the anti methyl group were shifted from $\delta 1.59 \rightarrow 1.25$ ($\Delta\delta = -0.34$). Again the deshielding effect is similar to that observed in the trans sulfoxides (57)-(61) (Table VI).



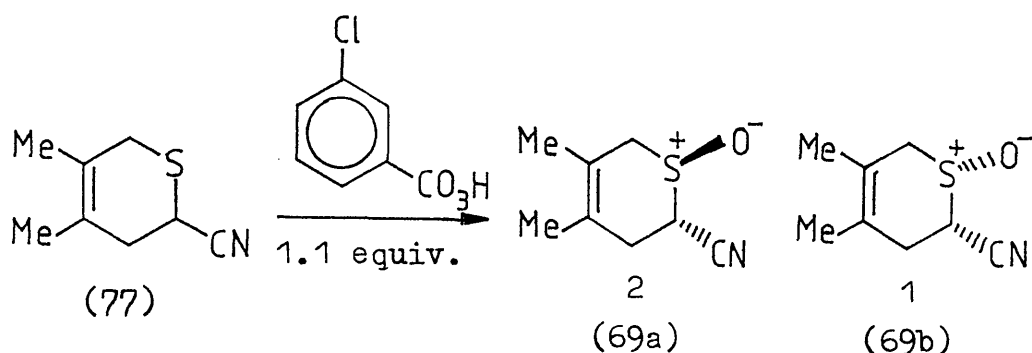
Determination of the stereochemistry of butadiene cycloadduct sulfoxides.

Determination of the stereochemistry of the sulphine cycloadducts of dimethylbutadiene was not so straightforward. The sulphides (74), (76) and (77) were prepared by the Bunte salt method⁵³, as used for the cyclopentadiene derivatives (52)-(56). Oxidation of both (74) and (76) gave ca. 1:4 mixtures of cis and trans sulfoxides (70a) and (70b) and (68a) and (68b), respectively (Scheme 77). Oxidation to give the sterically more stable trans sulfoxides would be

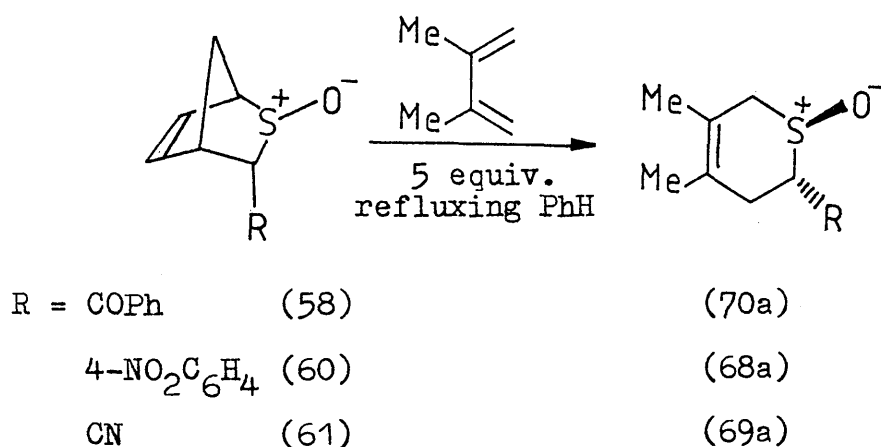
expected to be favoured; on this basis it seemed likely that the trans isomers (68a) and (70a) were the major products. Oxidation of the cyano derivative (77) gave a ca. 1:2 mixture of the cis and trans sulphoxides (69a) and (69b) (Scheme 78). The smaller ratio is to be expected for the sterically less demanding cyano group. Again it seemed likely that the major oxidation product (69b) had the trans stereochemistry. The sulphoxides (68a), (69a) and (70a) assigned the trans stereochemistry gave ^1H n.m.r. spectra identical to those of the products obtained when the corresponding trans cyclopentadiene cycloadduct sulphoxides (58), (60) and (61) were refluxed in benzene in the presence of five equivalents of 2,3-dimethylbuta-1,3-diene (Scheme 79). This provided strong evidence for the assignment of stereochemistry and showed that thermal 'transfer' of trans sulphines was stereospecific.



Scheme 77.



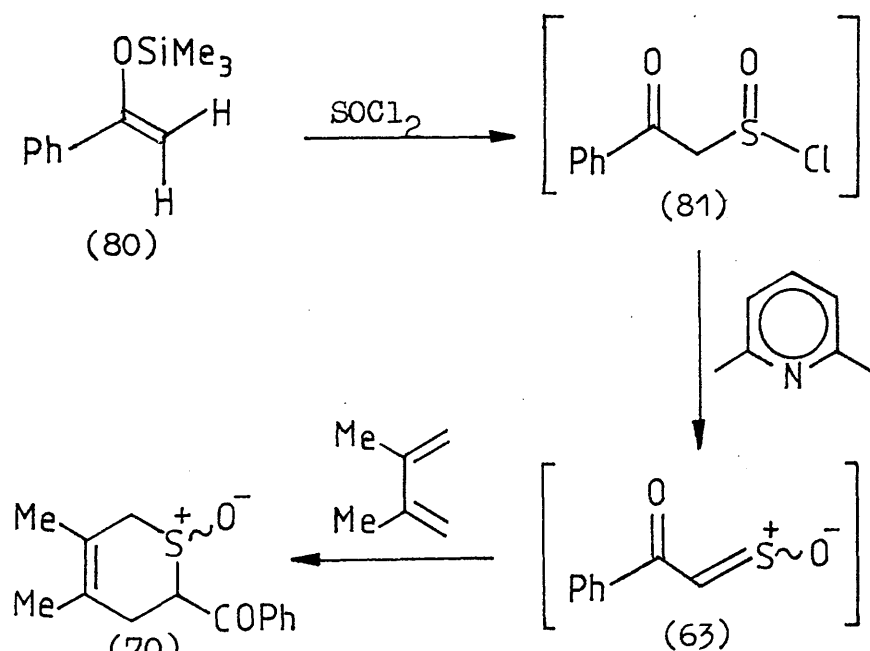
Scheme 78.



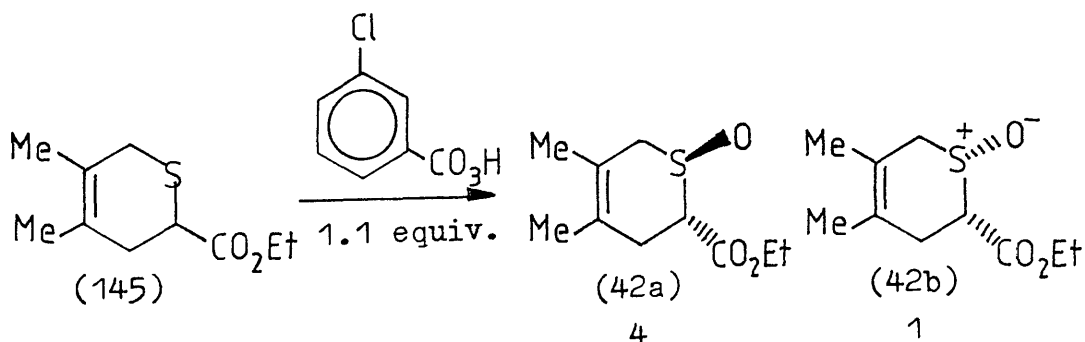
Scheme 79.

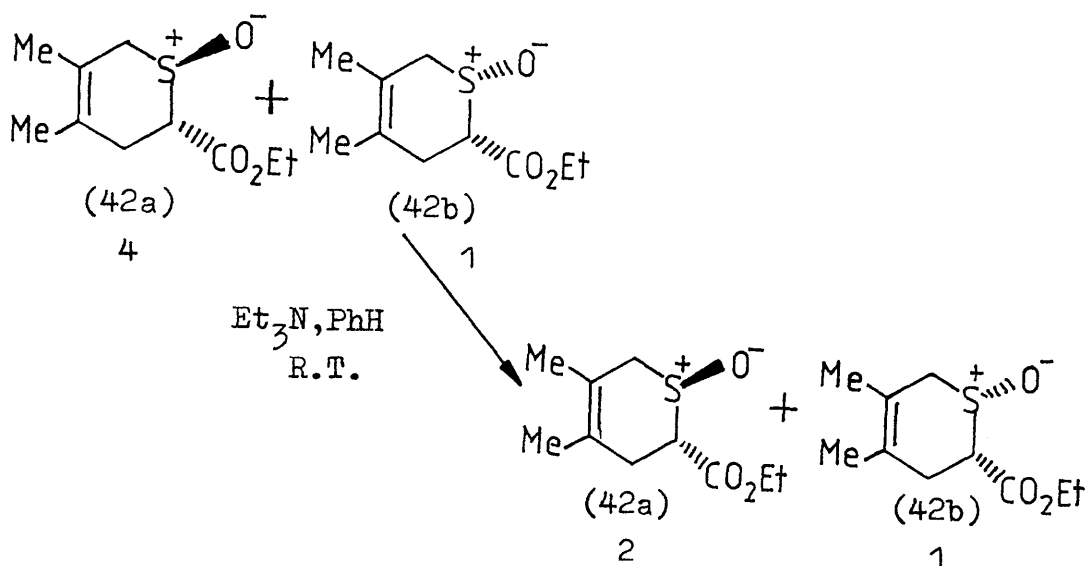
Zwanenburg et al.⁴¹ separated the crystalline sulfoxides (70a) and (70b), by fractional crystallisation. They prepared these by trapping the sulphines (63), generated by base induced dehydrochlorination of the sulphonyl chloride precursor (81), using 2,3-dimethylbuta-1,3-diene (Scheme 80). We found that the sulfoxides (68a) and (68b), which had not been previously prepared and which were not separable by chromatography, were also separated by fractional crystallisation. The non-crystalline sulfoxides (69a) and (69b) were likewise not separable by chromatography. When the sulfoxide mixture (68a) and (68b) was treated with one equivalent of triethylamine at room temperature the isomer (68b) was converted

completely into (68a). Lewis⁵² found that the sulphoxides (42a) and (42b), obtained as a ca. 4:1 mixture upon oxidation of the sulphide (145), were converted into a ca. 2:1 mixture upon similar treatment with triethylamine (Scheme 81). These observations provide further proof that (42a) and (68a) have the trans stereochemistry. The sulphoxide mixtures (69a) and (69b), and (70a) and (70b), obtained by oxidation of the corresponding sulphides as discussed above, were unaffected by triethylamine.

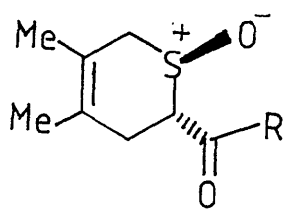


Scheme 80.





Scheme 81.



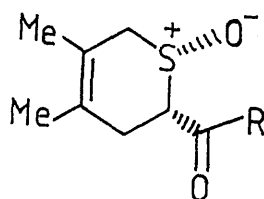
R = 4-MeC₆H₄ (146a)

4-MeOC₆H₄ (147a)

4-ClC₆H₄ (148a)

2-naphthyl (149a)

2-MeC₆H₄ (150a)



(146b)

(147b)

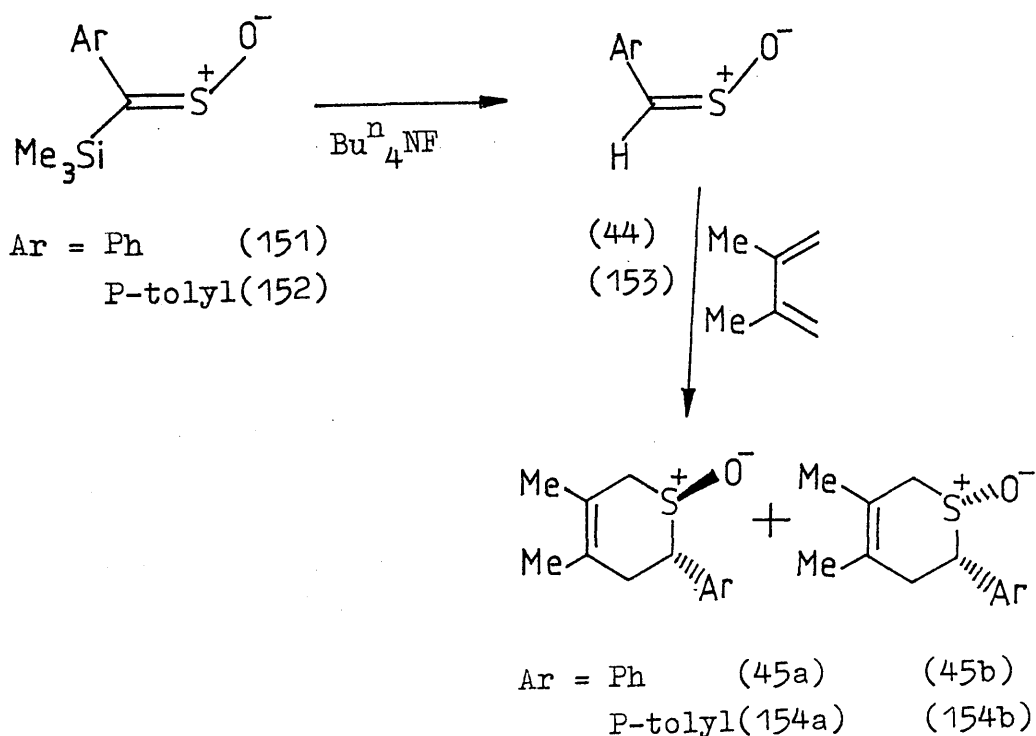
(148b)

(149b)

(150b)

Zwanenburg et al.⁴¹ found that there was no isomerisation of either the cis (146b)-(150b) or the trans (146a)-(150a) sulfoxides. They prepared these aroyl derivatives, as described for the benzoyl derivatives (70a) and (70b) (Scheme 80), from the corresponding silyl enol ethers. All, apart from (150a) and (150b) were purified by fractional crystallisation.

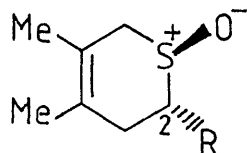
They tentatively assigned the stereochemistry of these sulphoxides from their ^1H n.m.r. spectra. However, at that time methods for the synthesis of the corresponding sulphides were not available. They were therefore unable to prepare mixtures of the isomeric sulphoxides by oxidation of the sulphides, to give presumably trans sulphoxides as major products. They pointed out however that the sulphoxides formed two classes identifiable by their ^1H n.m.r. spectra. One class, which we have now confirmed to be the trans isomers, showed two similar vicinal coupling constants, $\underline{J}_{2,3}$ ca.6-9Hz. The other class, the cis isomers, showed two different vicinal coupling constants, $\underline{J}_{2,3}$ ca.9-10 and ca.3-4Hz.



Scheme 82.

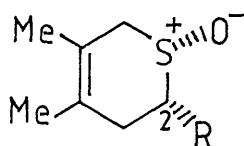
Bonini et al.¹⁷ prepared the sulphoxides (45a) and (45b), and (154a) and (154b) by trapping the cis sulphines (44) and (153), formed by desilylation of the precursors (151) and (152), at room temperature, using 1.5 equivalents of 2,3-dimethylbuta-1,3-diene (Scheme 82). They found that, for the trans sulphoxides (45a) and (154a), the ¹H n.m.r. signals for the 2-H protons syn to the sulphoxide group were shifted downfield with respect to the corresponding signal in the parent sulphides, presumably because of the deshielding effect brought about by the positive centre of the sulphoxide dipole. In contrast, for the cis sulphoxides (45b) and (154b), having 2-H anti to the sulphoxide group, an upfield shift was observed. For example, for (45a) the 2-H signal was observed at δ 4.12, for (45b) at δ 3.73 and in the sulphide (123) at δ 3.98. Similar shifts are observed for the sulphoxides (45) and (67)-(70), including those prepared in the present study (Tables VIII and IX). Further evidence for the classification of the various sulphoxides as cis and trans isomers was obtained from the 2-H and 3-H₂ coupling constants as discussed earlier. In all cases $J_{2,3}$ for the trans isomers were ca. 6-9Hz, whereas for the cis isomers the coupling constants were ca. 9-10hz and 3-4hz.

Table VIII. ^1H chemical shifts $[\delta(\text{CDCl}_3)]$ for dimethylbutadiene cycloadducts and their trans-sulphoxides.



R	2-H(S)		2-H(SO)		$\Delta\delta(\text{S} \rightarrow \text{SO})$
CO_2Et	(145)	3.54^{53}	(42a)	3.75^{39}	+0.21
COPh	(74)	4.50^{53}	(70a)	4.80	+0.30
$4\text{-BrC}_6\text{H}_4\text{CO}$	(75)	4.42	(67a)	4.73	+0.31
$4\text{-NO}_2\text{C}_6\text{H}_4$	(76)	4.06^{53}	(68a)	4.11	+0.05
CN	(77)	3.76^{53}	(69a)	3.98	+0.22
Ph	(123)	3.98^{66}	(45a)	4.12	+0.14

Table IX. ^1H chemical shifts $[\delta(\text{CDCl}_3)]$ for dimethylbutadiene cycloadducts and their cis-sulphoxides.



R	2-H(S)		2-H(SO)		$\Delta\delta(\text{S} \rightarrow \text{SO})$
CO_2Et	(145)	3.54^{53}	(42b)	3.33^{39}	-0.11
COPh	(74)	4.50^{53}	(70b)	4.43	-0.07
$4\text{-NO}_2\text{C}_6\text{H}_4$	(76)	4.06^{53}	(68b)	3.96	-0.10
CN	(77)	3.76	(69b)	3.72	-0.04
Ph	(123)	3.98^{66}	(45b)	3.73	-0.25

The much smaller chemical shift differences ($\Delta\delta$), and their different sign, found for the trans butadiene cycloadduct sulphoxides (42a), (45a) and (67a)-(70a) (Table VIII) compared with the trans cyclopentadiene cycloadduct sulphoxides (57)-(61) (Table IV) can be rationalised from an inspection of molecular models. In the trans cyclopentadiene cycloadduct sulphoxides, the methylene bridge imposes a 'boat-like' conformation on the thiopyran ring, so that the 3-H and syn sulphoxide bonds are eclipsed. In contrast, in the trans butadiene cycloadduct sulphoxides this restriction is not imposed and the conformation is 'chair-like' with 2-H close to the positive end of the sulphoxide dipole and no longer close to the negative oxygen. Hence 2-H is deshielded and a downfield shift is observed with respect to the same signal in the corresponding sulphide. In the corresponding cis butadiene cycloadduct sulphoxides (42b), (45b) and (68b)-(70b), the more stable 'chair-like' conformation has 2-H syn to the sulphur lone pair and a slight shielding effect is observed.

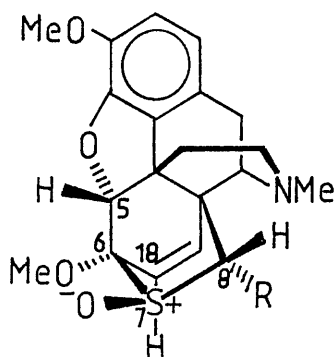
Determination of the stereochemistry of thebaine cycloadduct sulphoxides.

For the thebaine adducts (133) and (134) negative shifts were observed for the 8-H signals, syn to the sulphoxide oxygen, with respect to the corresponding signals of the sulphides (Table X). These shielding effects resemble those in the related cyclopentadiene adducts (Table IV). The 18-H protons β to the

sulphoxide are also shielded. The deshielding effects of the sulphoxide oxygen on 5-H is to be expected for the stereochemistry proposed [see the shifts for 7-H in the cyclopentadiene adducts (Table VI)] Thus these adducts have the trans stereochemistry as shown.

Table X. ^1H chemical shifts [$\delta(\text{CDCl}_3)$] for thebaine adducts and their trans sulphoxides.

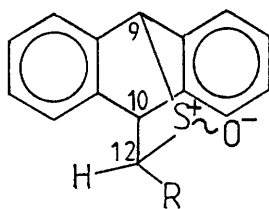
R	CO_2Et		$4\text{-NO}_2\text{C}_6\text{H}_4$	
8-H(S)	(135)	5.23	(136)	5.80
8-H(SO)	(133)	4.73	(134)	5.13
$\Delta\delta(\text{S}\rightarrow\text{SO})$		-0.50		-0.67
18-H(S)	(135)	6.21	(136)	6.37
18-H(SO)	(133)	5.67	(134)	5.99
$\Delta\delta(\text{S}\rightarrow\text{SO})$		-0.54		-0.38
5-H(S)	(135)	4.98	(136)	5.08
5-H(SO)	(133)	5.51	(134)	5.64
$\Delta\delta(\text{S}\rightarrow\text{SO})$		+0.53		+0.56



Determination of the stereochemistry of anthracene cycloadduct sulphoxides.

As observed for the cyclopentadiene cycloadduct sulphoxides (Tables IV and V), the 12-H n.m.r. signals in the anthracene cycloadduct trans sulphoxides were shifted upfield relative to those in the sulphides by ca. 1p.p.m., whereas for the cis sulphoxide the shift in the same direction was appreciably less (Table XI). The relative configurations of the ethyl ester derivatives (95) had already been proposed³⁹ on the basis of base-catalysed epimerisation experiments. Moreover, all the isomers (41a) and (119a)-(122a) were formed as the major products by oxidation of the corresponding sulphides. The large shielding effects, $\Delta\delta(S \rightarrow SO)$ ca. -1 shown by protons syn to, and eclipsed by, S-O groups is therefore of diagnostic value generally.

Table XI. ¹H chemical shifts [$\delta(CDCl_3)$] for anthracene cycloadducts and their sulphoxides.



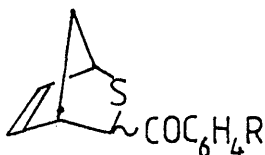
R	12-H(S)		12-H(SO)		$\Delta\delta(S \rightarrow SO)$
CO ₂ Et	(95)	4.12 ⁶³	<u>trans</u> -(41a)	3.11 ³⁹	-1.01
C ₆ H ₅	(104)	4.49	<u>trans</u> -(120a)	3.42	-1.07
4-NO ₂ C ₆ H ₄	(100)	4.48	<u>trans</u> -(119a)	3.53	-0.95
4-BrC ₆ H ₄ CO	(109)	4.58	<u>trans</u> -(121a)	3.78	-0.80
CH ₂ CH ₃	(114)	3.25	<u>trans</u> -(122a)	2.22	-1.03
CO ₂ Et	(95)	4.12 ⁶³	<u>cis</u> -(41b)	3.90 ³⁹	-0.22
CH ₂ CH ₃	(114)	3.25	<u>cis</u> -(122b)	2.86	-0.39

3. Conclusions.

A variety of trans sulphines have been generated on a preparative scale as reactive intermediates. The appropriate thioaldehydes were trapped using anthracene and cyclopentadiene and the resulting thioaldehyde adducts were oxidised to give the sterically more favourable trans sulfoxide products. These dissociated thermally to liberate the trans sulphines by retro-Diels-Alder reactions at moderate (ca.80°C) temperatures. From studies involving thermal 'transfer' of the trans sulphines $RCH=SO$ ($R=CO_2Et, 4-BrC_6H_4CO, 4-NO_2C_6H_4, C_6H_5$ or CN) from cyclopentadiene or anthracene adducts to dimethylbutadiene, the rates of transfer were shown to be dependent on both the steric and electronic effects of the α -substituents, R.

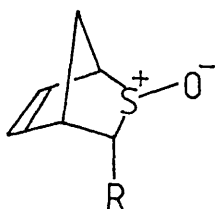
Although initially it was expected that cis sulphines could similarly be generated from cis sulfoxides, prepared by oxidation of thioaldehyde adducts, this was not realised in practice. For the series of cyclopentadiene thioaldehyde adducts prepared, the endo and exo sulphine precursors were not generally easy to separate. Only the keto substituted sulphides (52) and (53) could be separated by chromatography. Unfortunately the cis sulfoxide (78), formed as the sole sulfoxide product upon oxidation of cis-(53), epimerised to give a mixture of the sulfoxides (78) and (59) when its purification was attempted on a silica or a fluorosil column. Unlike the trans sulphine,

trans 4-BrC₆H₄COCH=SO, which was released upon dissociation of the cyclopentadiene sulphoxide (59) in refluxing benzene, the cis sulphine cis 4-BrC₆H₄COCH=SO was not released under similar conditions from a 'crude' sample of its sulphoxide precursor (78). A similar observation had been made with the ethyl ester derivatives³⁹ (57) and (83). This serves as further evidence that trans sulphines are transferred more easily than cis sulphines. For the series of anthracene thioaldehyde adducts prepared, generally the size of α -substituents seemed to prevent formation of significant amounts of the sterically disfavoured cis sulphoxides. Only for the ethyl derivative (114) were the two sulphoxides formed in comparable amounts, as had been observed for the ethyl ester³⁹ (95). It was not possible to separate the cis, trans sulphoxide mixture of propanethial adducts (122). When these two sulphoxides were heated with dimethylbutadiene in refluxing toluene both were recovered unchanged. In o-dichlorobenzene at 140°C, however, they reacted to give the sulphoxide products (127) in low yield. The cis:trans ratio of the dimethylbutadiene sulphoxides (127) could not be determined by n.m.r. spectroscopy.



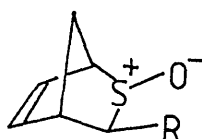
R = H (52)

Br (53)



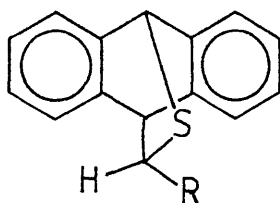
R = CO₂Et (57)

4-BrC₆H₄CO (59)



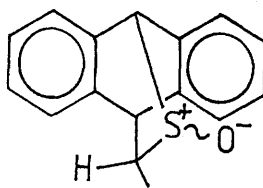
(83)

(78)



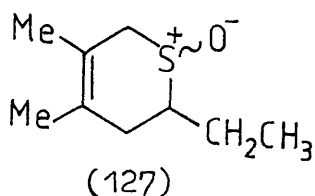
R = CO₂Et (95)

CH₂CH₃ (114)



(41)

(42)



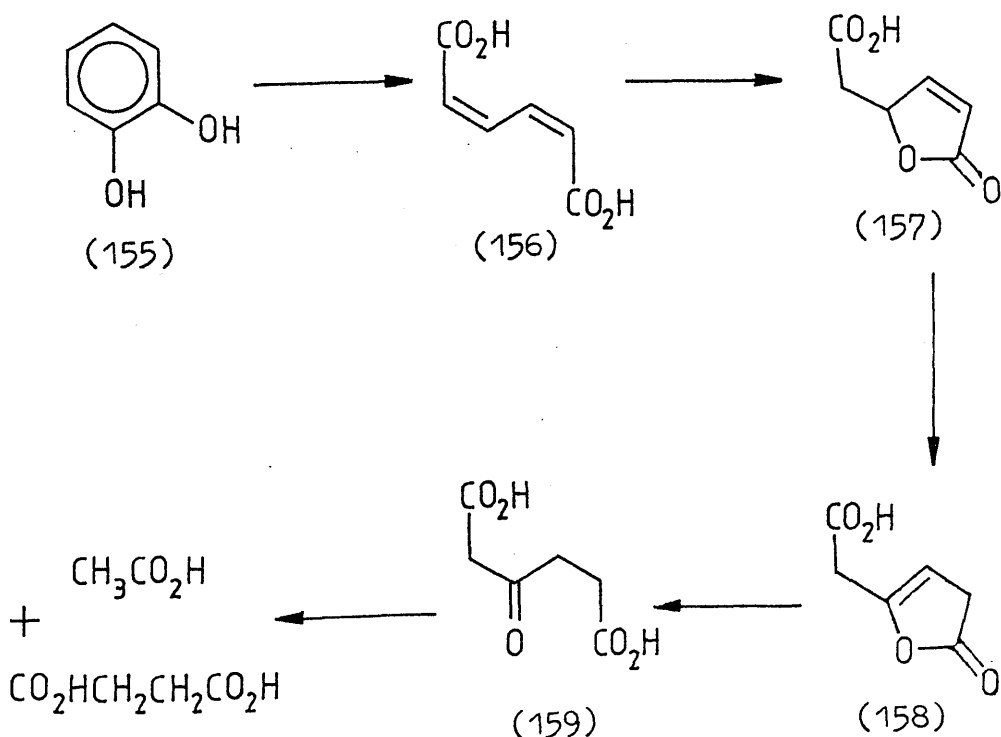
(127)

In all cases, thermal transfer of trans sulphines from cyclopentadiene or anthracene cycloadducts to dimethylbutadiene, occurred with complete retention of stereochemistry, as expected for concerted [4+2] retro-cycloaddition and cycloaddition reactions. Also, these experiments showed that a range of trans sulphines, RCH=SO (R=CO₂Et, 4-BrC₆H₄CO, 4-NO₂C₆H₄, C₆H₅ or CN) retained their stereochemical integrity at the temperatures, and for the short times of their independent existence, during the 'transfer' experiments.

CHAPTER 2.

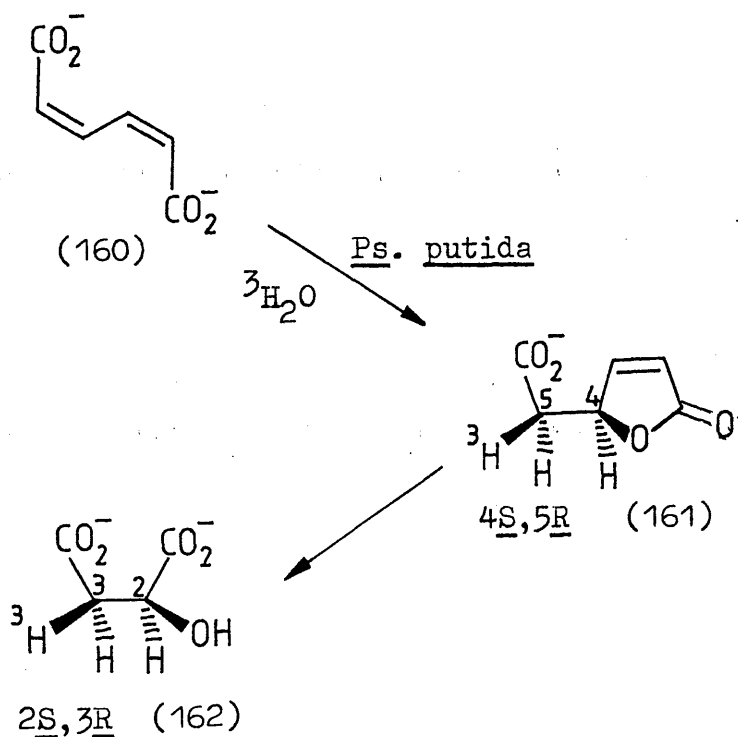
Biosynthetic Transformations Involving Muconolactones.

A number of benzene derivatives present in soil or industrial wastes are degraded via the muconic acid pathways⁷⁴. In the simplest case, pyrocatechol (155) formed by the decay of plant debris and the like is converted by bacteria or fungi with uptake of oxygen to cis,cis-muconic acid (156) which is cyclised enzymically to the muconolactone (157). It is then transformed via the enol lactone (158) to 3-oxoadipic acid (159) which is further degraded to the metabolically useful acetic and succinic acids (Scheme 83).



Scheme 83.

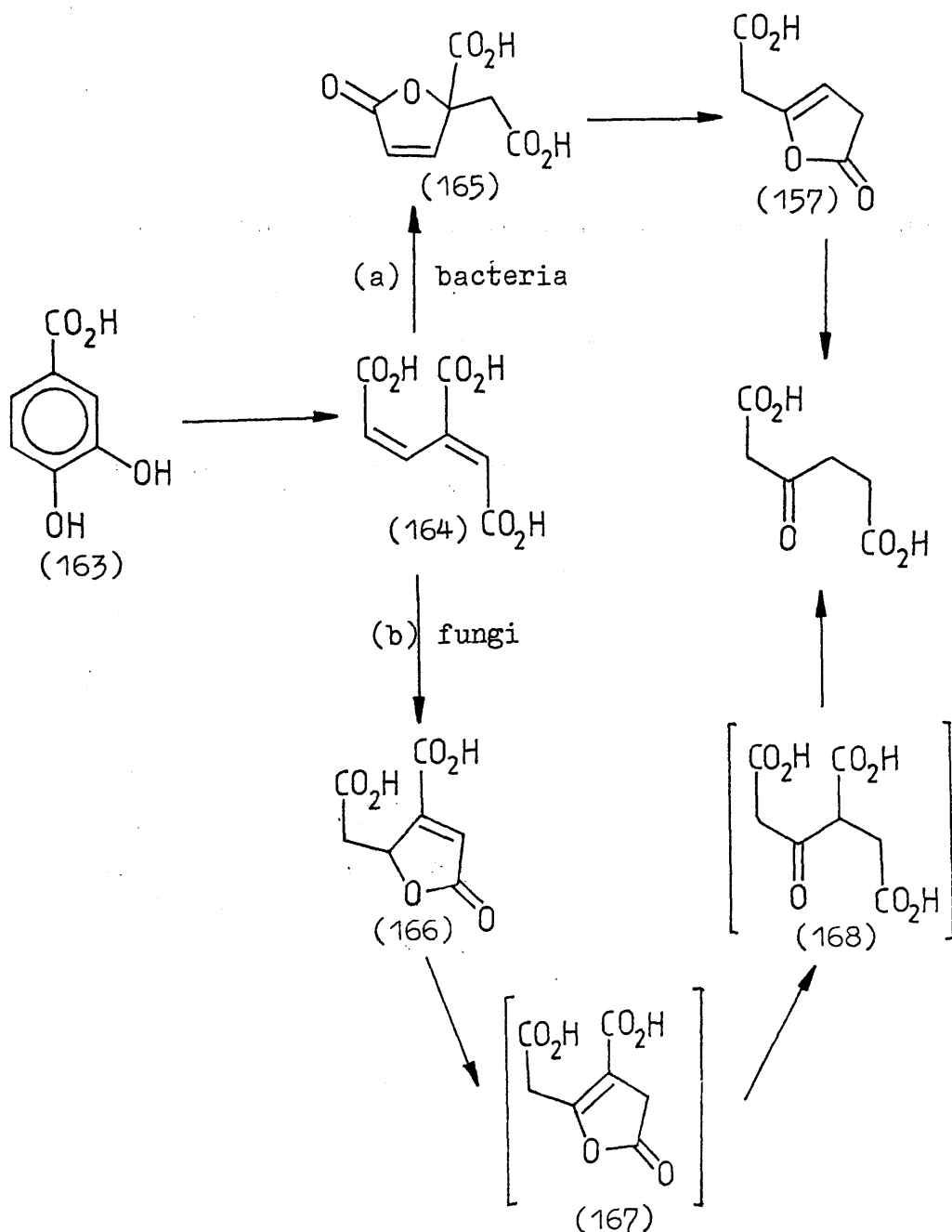
In 1969, Avigad and Englard⁷⁵ determined the absolute stereochemical course of muconate cycloisomerase from Pseudomonas putida. By feeding the cis,cis-muconate (160) in tritiated water to the Pseudomonas cultures, they obtained the 5- $[\text{}^3\text{H}]$ -muconolactone (161) which they oxidised chemically to the (2S,3R)- $[\text{}^3\text{H}]$ malate (162)(Scheme 84). Thus they showed that the cycloisomerase product was the (4S,5R)- $[\text{}^5\text{}^3\text{H}]$ muconolactone, formed by cyclisation with syn addition.



Scheme 84.

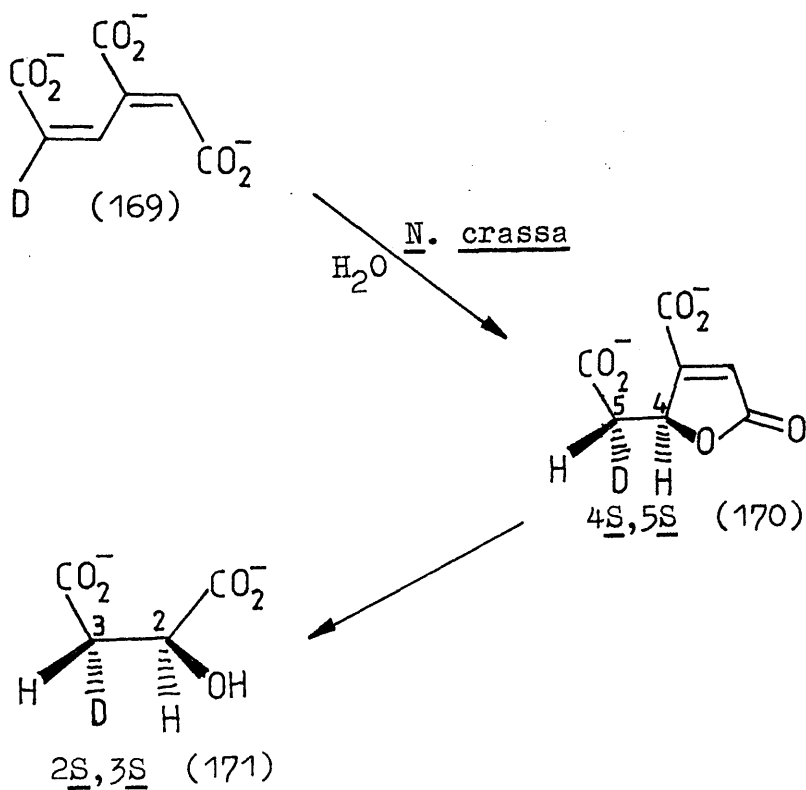
The corresponding carboxymuconate pathway has been more widely studied⁷⁶⁻⁷⁹. Here there are two possible modes of cyclisation of the 3-carboxy-cis,cis-muconic acid (164), leading to two isomeric muconolactones (165)

and (166). It so happens that in bacteria^{76,77} path (a) is followed giving the 4-carboxymuconolactone (165), whereas in fungi^{78,79} 3-carboxymuconolactone (166) is the product, formed by path (b). These are converted to 3-oxoadipic acid via (157), (167) and (168) (Scheme 85). Stanier and Ornston⁸⁰ found that the enol lactone (157) was readily formed by spontaneous decarboxylation of (165). Kirby et al.⁷⁹ likewise obtained good evidence for the intermediates (167) and (168) in the fungal pathway.



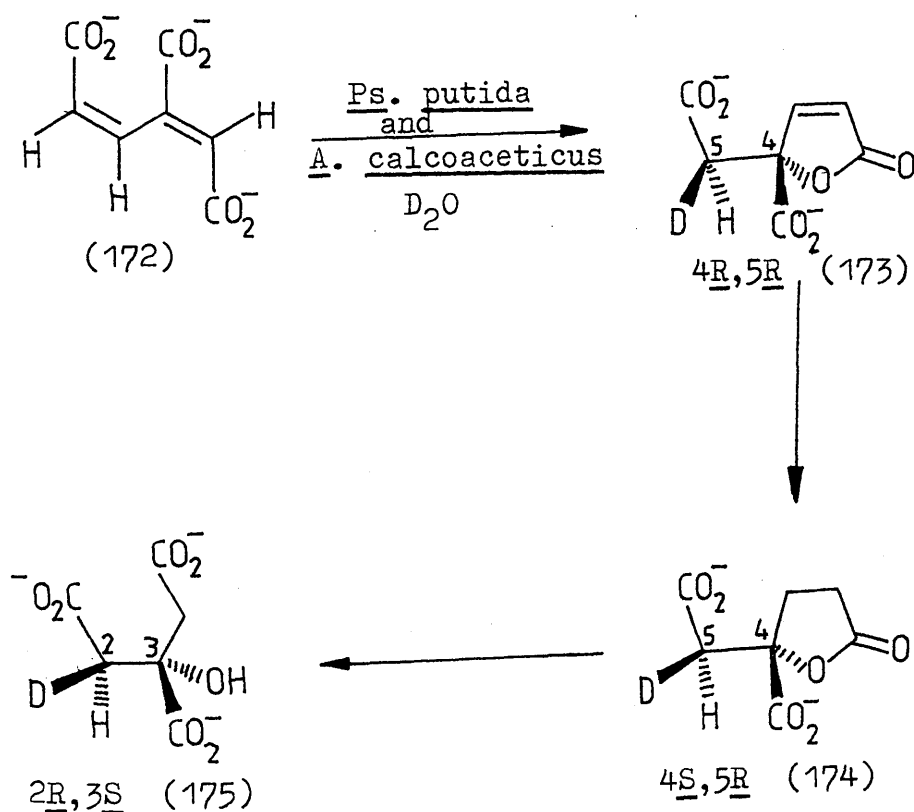
Scheme 85.

In 1975, Kirby et al.⁷⁸ determined the absolute stereochemistry of the cyclisation of (164) to (166) catalysed by the fungus Neurospora crassa. In a manner complementary to that of Avigad and England⁷⁵ they incubated the deuterio muconate (169) with a crude preparation of the lactonising enzyme from N. crassa SY4a, isolated the resulting lactone (170), then degraded this by successive treatment with ozone, manganese dioxide and formic acid-hydrogen peroxide to obtain the (2S,3S)-[3-²H]malate (171) (Scheme 86). Thus, as with the simple muconolactone, they likewise proved the 3-carboxymuconolactone had been formed by syn addition and had the (4S,5S) configuration.



Scheme 86.

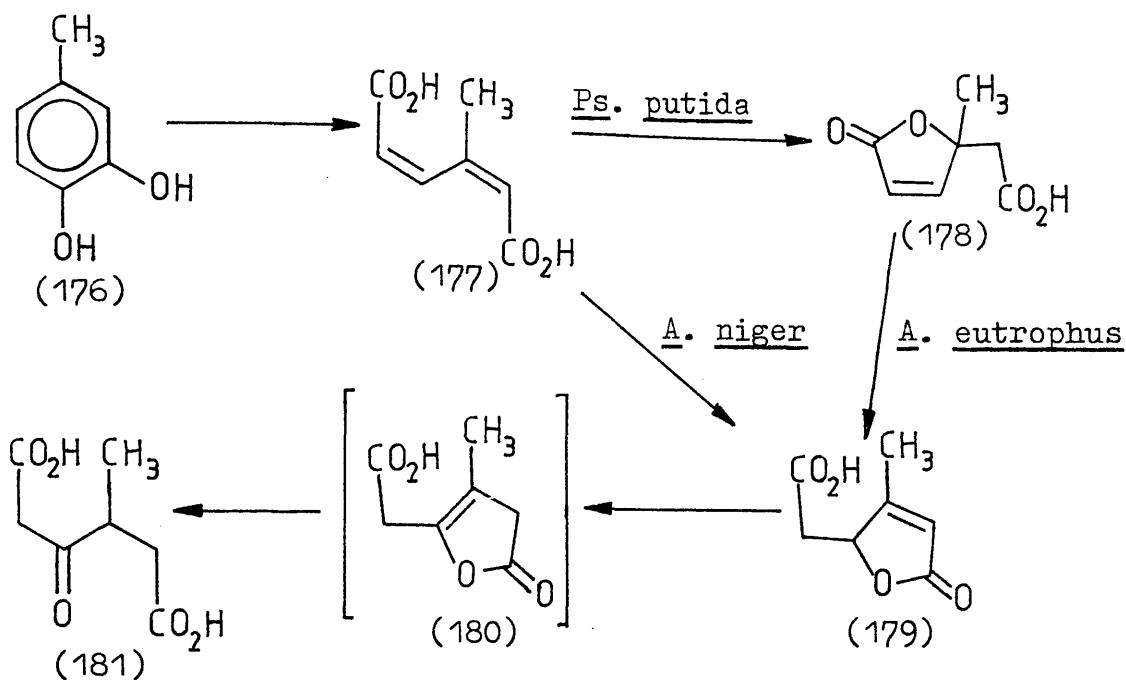
In contrast, Zocharich et al.⁷⁶ have recently found that anti cyclisation was involved in the production of the 4-carboxymuconolactone (173) from 3-carboxymuconate in deuterium oxide using both Pseudomonas putida and Acinetobacter calcoaceticus. On account of its instability, the absolute configuration of (173) was determined by reductive trapping. Thus catalytic hydrogenation, followed by chemical degradation of the resulting [5-²H]homocitrate lactone (174) gave the [2-²H]citrate (175) (Scheme 87). Stereochemical analysis⁷⁶ showed that (175) had the (2_R,3_S) configuration and hence that (173) had the (4_R,5_R) configuration.



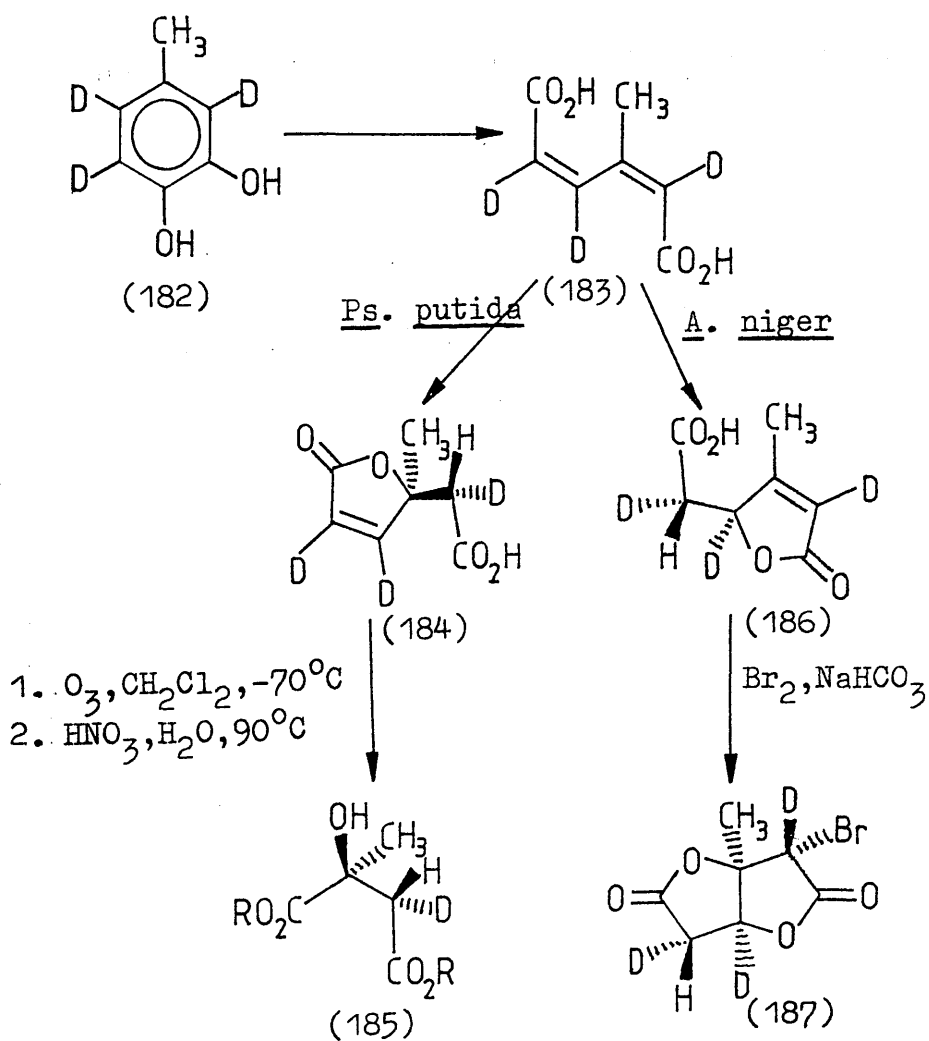
Scheme 87.

Powlowski and Dagley⁸¹ found that toluene, p-cresol and p-toluic acid are degraded via 4-methylpyrocatechol (176) and hence 3-methyl-cis,cis-muconic acid (177) (Scheme 88). In the yeast Trichosporon cutaneum⁸¹ this 3-methylmuconic acid is converted into 3-methylmuconolactone (179) and thence 4-methyl-3-oxoadipic acid (181), presumably via (180). Catelani et al.⁸² found that the 4-methylmuconolactone (178) was essentially a metabolically 'dead-end' product, since there was no free proton to undergo the shift of the muconate isomerase reaction giving rise to the enol lactone (180). Unexpectedly, strains of Alcaligenes eutrophus and several nocardioform actinomycetes (bacteria), e.g. Rhodococcus ruber, have recently been shown⁸³ to effect the enzymic transformation of 4-methylmuconolactone (178) into 3-methylmuconolactone (179) thereby overcoming the 'bacterial block', although in the fungus Aspergillus niger there is no comparable enzymic activity. Thus the methyl muconolactone pathway can be written as in Scheme 88.

Recently Kirby et al.^{84,85} have shown that enzyme-catalysed cyclisation of 3-methyl-cis,cis-muconic acid proceeds by syn addition of a carboxyl group to the double bond to form the 3-methylmuconolactone (186) in Aspergillus niger and the 4-methylmuconolactone (184) in Pseudomonas putida (Scheme 89). They fed the deuteriated pyrocatechol (182) to a mutant strain of A. niger known to accumulate 3-methylmuconolactone (Scheme 89). This gave, via the muconic acid (183), the muconolactone (186), which was



Scheme 88.

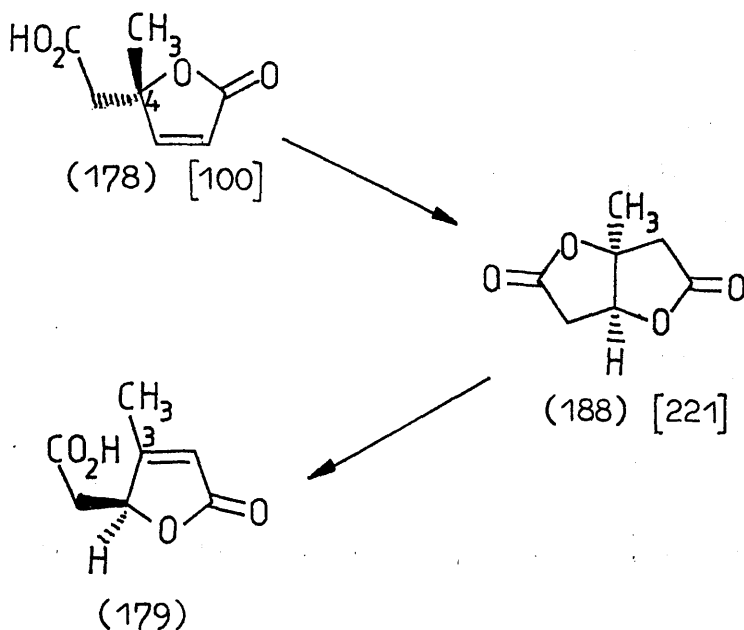


Scheme 89.

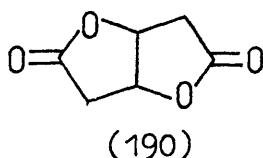
converted to the bromodilactone (187). This was shown to have the stereochemistry indicated (i.e. 4S,5R) by unambiguous assignment of the 4-H signal of its ^1H n.m.r. spectrum^{84,85} relative to the signals of that of the corresponding undeuteriated bromodilactone (187; D=H). (The absolute stereochemistry of undeuteriated methylmuconolactone (186; D=H) had been determined unambiguously by X-ray crystallography⁸⁴ and that of the undeuteriated methylbromodilactone (187; D=H) had been determined by chemical correlation⁸⁴). When the pyrocatechol (182) was likewise fed to Pseudomonas putida, the muconolactone (184) was isolated. The stereochemistry of (184) was established by degradation, upon treatment with ozone and nitric acid⁸⁷, to give (S)-citramalic acid (185; R=H) which was then esterified. This ester (185; R=Me) was shown to have the configuration indicated by ^1H n.m.r. spectroscopic comparison with an authentic sample⁸⁸. Thus (184) was shown to have the (4S,5S) configuration (Scheme 89).

The conversion of 4-methylmuconolactone (178) into 3-methylmuconolactone (179) in certain specialised species of bacteria might occur via the bicyclic dilactone intermediate (188) (Scheme 90). Cain et al.⁸⁹ found that the dilactone (188) and (+)-4-methylmuconolactone (178) served as substrates for 4-methylmuconolactone methyl isomerase from Rhodococcus ruber N75 (nocardioform actinomycete), with the relative conversion rates shown in square brackets in Scheme 90. In contrast cis,cis-methylmuconic acid (177) and the cis,trans isomer (189)

were found not to be substrates. Remarkably, the parent dilactone (190) was also a good substrate for the isomerase enzyme⁹⁰.



Scheme 90.

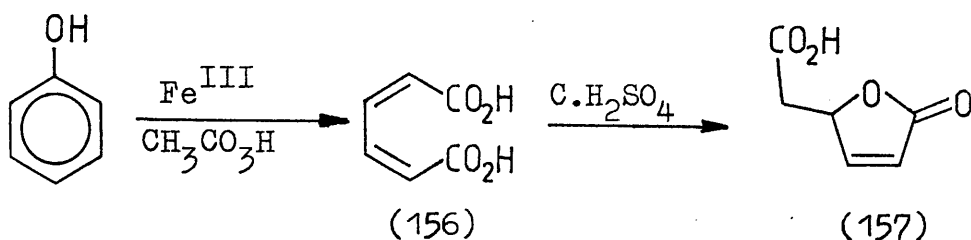


The present work aimed to extend current studies on the methylmuconate pathways^{84,85} (Scheme 88), by experiments with higher alkyl homologues of known substrates. For this purpose, the synthesis of various ethyl and n-propyl derivatives was undertaken. Also, an attempt to resolve the parent muconolactone was made to provide (a) a convenient supply of both natural and unnatural enantiomers and (b) a source of both enantiomers of the corresponding dilactone, a known substrate for the methyl-lactone isomerase enzyme.

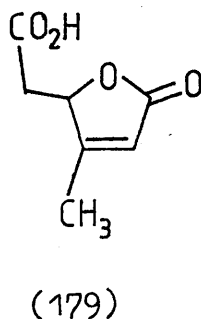
2. Discussion of Results.

Preparation and attempted resolution of muconolactone (157)

cis,cis-Muconic acid (156) was prepared by the procedure reported by Pandell⁹¹ by iron (III)-catalysed oxidation of phenol using peracetic acid. This was then cyclised in the presence of concentrated sulphuric acid⁹² to give the muconolactone (157) (Scheme 91).



Scheme 91.

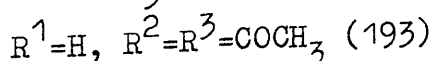
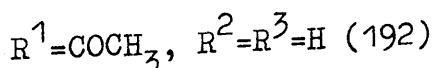
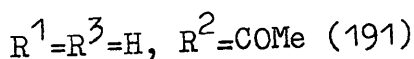
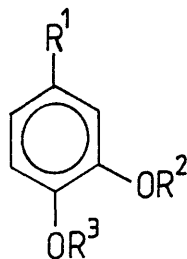


Kirby et al.⁸⁴ found that (\pm) 3-methylmuconolactone (179) was resolved by repeated fractional crystallisation of the diastereoisomeric salts of (S)-(-)-1-phenylethylamine. Attempted resolution of (\pm)-(157) by this method, however, was not successful. Crystals of the diastereoisomeric salts of (S)-(-)-1-phenylethylamine with (\pm) muconolactone

were obtained and further recrystallised. The melting point and optical rotation of the crystalline salts recovered after many recrystallisations, however, indicated that resolution had not been achieved.

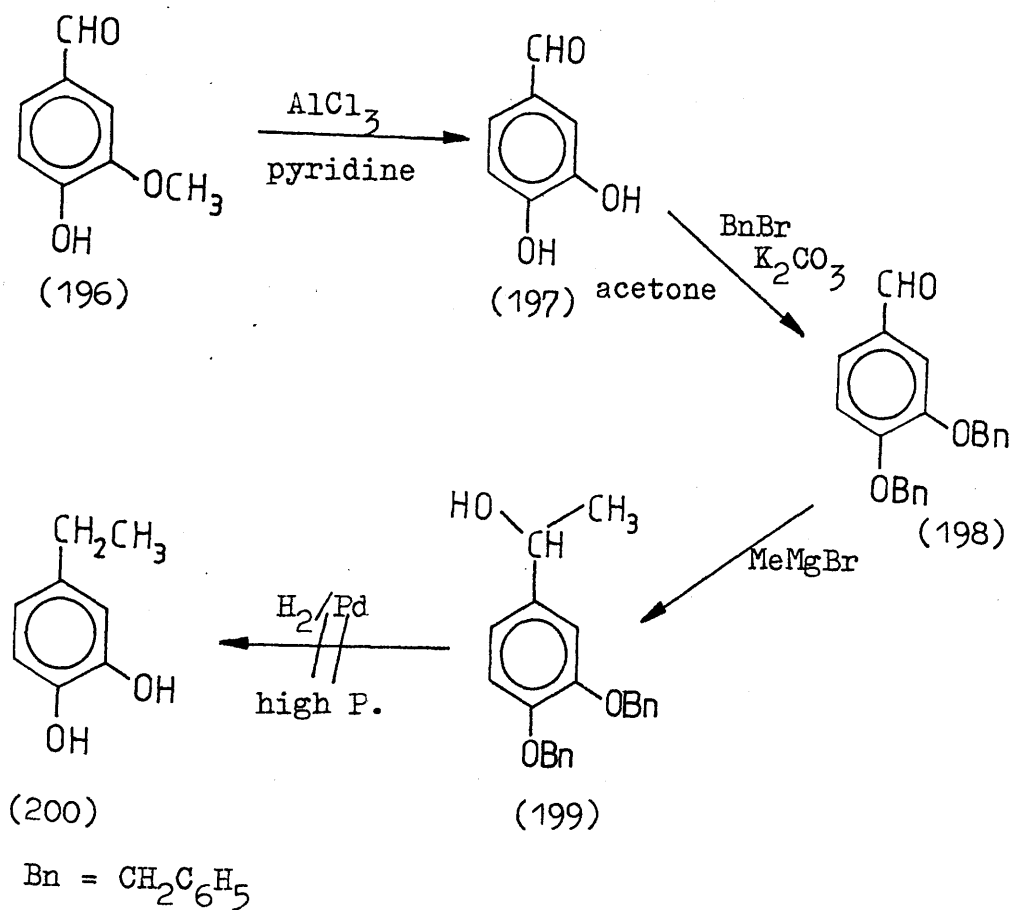
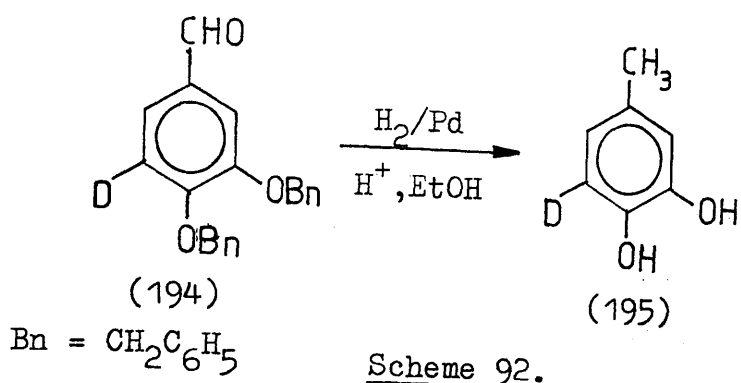
Preparation of 4-ethylpyrocatechol.

Initially two routes seemed feasible for the synthesis of 4-ethylpyrocatechol. It was thought that Fries rearrangement of the phenol ester (191) followed by reduction of the acetylcatechol (192) would be a good route to 4-ethylpyrocatechol. Esterification of pyrocatechol however gave a mixture of the monoester (191), diester (193) and unreacted pyrocatechol. Attempted separation of the diester from the monoester and pyrocatechol using sodium hydroxide resulted in hydrolysis to give increased amounts of pyrocatechol. The three products were however separable on a short silica column using chloroform as elutant to give (191) in 16% yield. On account of the low yield of the desired product and the fact that the Fries rearrangement would give a mixture of products which might be difficult to separate, an alternative route was sought.



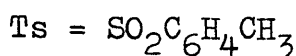
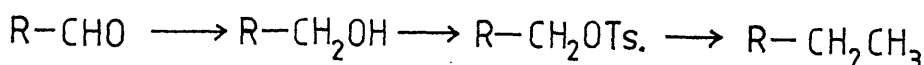
Kirby and Ogunkoya⁹³ had prepared the deuteriated methylpyrocatechol (95) by hydrogenation of the benzylated intermediate (194) (Scheme 92). Thus it was thought that 4-ethylpyrocatechol (200) might be prepared by hydrogenation of the benzyl-protected benzyl alcohol (199). Demethylation of vanillin (196) by the method of Lange⁹⁴ using pyridine and aluminium chloride gave protocatechualdehyde (197). This was then protected using two equivalents of potassium carbonate and two equivalents of benzyl bromide in acetone to give the aldehyde (198). Upon reaction of (198) with methyl magnesium bromide, the ethyl alcohol (199) was obtained which was then hydrogenated in ethanol using a palladium/carbon catalyst (Scheme 93). Repeatedly, however, no 4-ethylpyrocatechol (200) was obtained, even at high pressures. ¹H N.m.r. spectroscopy showed that the product formed had been debenzylated but otherwise the spectrum was complicated, with broad signals which may be due to the presence of polymeric material. In the presence of a catalytic amount of acid, a red gum was isolated which was also difficult to identify. Better results may be obtained by using higher temperatures or with the use of an alternative catalyst, however, these experiments were not attempted.

In order to overcome the difficult hydrogenation stage, it was planned to interconvert the aldehyde functional group to an ethyl group in the alternative manner shown in Scheme 94, i.e. reduction of the aldehyde

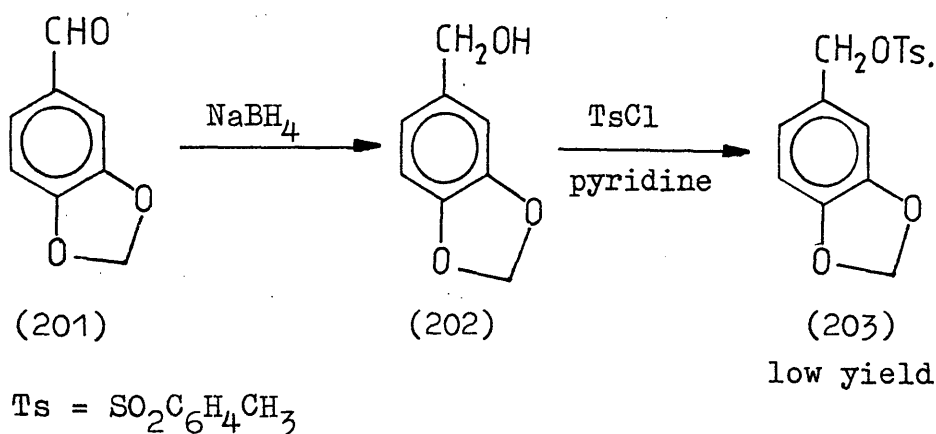


to the alcohol, formation of the corresponding tosylate and then substitution using methyl magnesium

bromide to give the ethyl group. Thus piperonal (201) was reduced using sodium borohydride or lithium aluminium hydride to piperonyl alcohol (202) which was then treated with tosyl chloride and pyridine in dry THF to give the tosylate (203) (Scheme 95). Repeatedly, however, the yield of tosylate formed was very low (<10%), possibly because of the destabilising effect of the para phenolic oxygen.



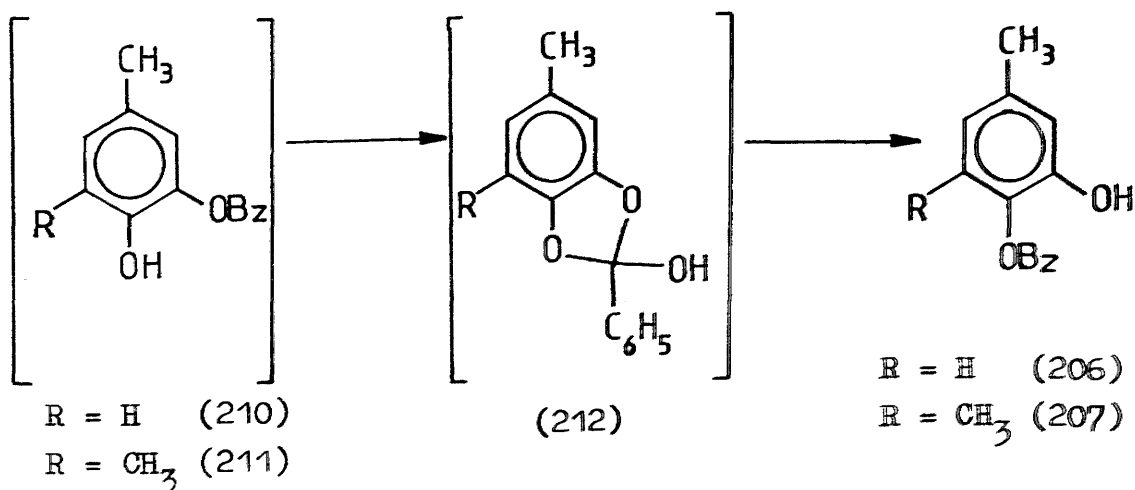
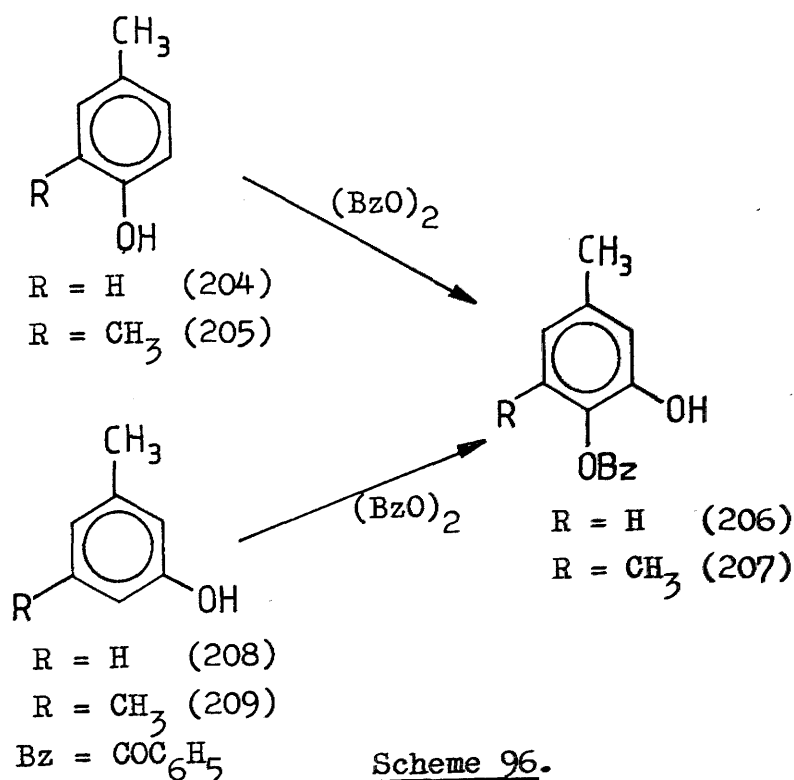
Scheme 94.



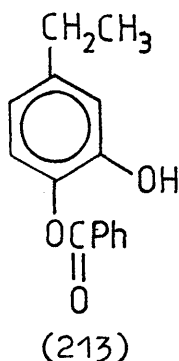
Scheme 95.

Of the many other possible synthetic routes considered, one seemed most promising. Cosgrove and Waters⁹⁵ showed that a variety of monohydric phenols react with benzoyl peroxide in boiling chloroform to give the monobenzoates of pyrocatechol derivatives. Furthermore they showed that para (204) and meta (208)

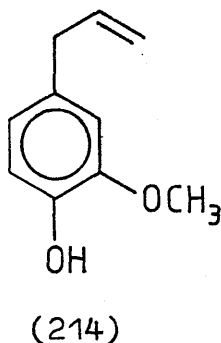
cresol gave the same product (206) as did meta-4 (209) and meta-5 (205) xylenol which gave (207), confirming these assertions by independent syntheses (Scheme 96). They suggested that, with p-cresol (204) and m-5-xylenol (205), the para substituted esters are formed by molecular rearrangement of the initially formed meta substituted esters (210) and (211), possibly via the intermediate (212) (Scheme 97).



Thus 4-ethylphenol was heated under reflux in chloroform in the presence of one equivalent of benzoyl peroxide for 8h to give the monoester (213), assumed to be para substituted, which was then hydrolysed using aqueous sodium hydroxide to give 4-ethylpyrocatechol in 68% yield.

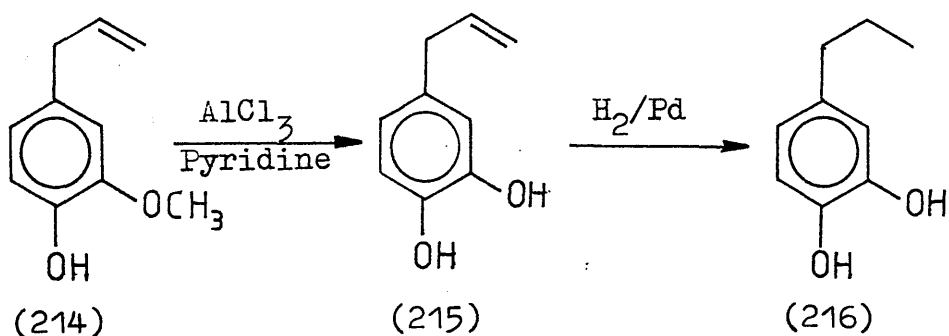


Preparation of 4-n-propylpyrocatechol.



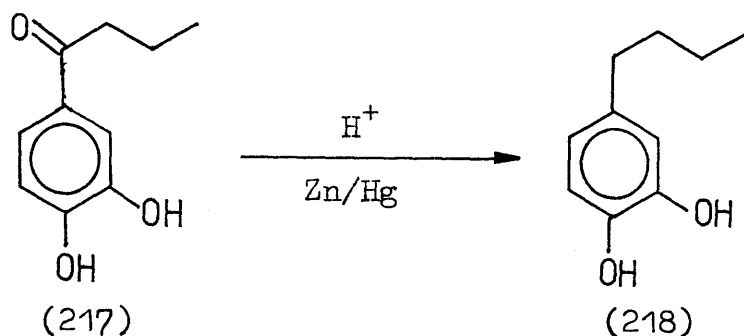
Eugenol (214), a constituent of cloves, was considered as a possible precursor to 4-n-propylpyrocatechol. It was thought that it would be readily converted to 4-n-propylpyrocatechol in two stages viz; hydrogenation of the double bond followed by demethylation. It was expected that the

method of Lange⁹³ would be satisfactory for the demethylation of eugenol, i.e. demethylation using pyridine and aluminium chloride (Scheme 98). Eugenol (214) was converted in this way into a ca. 1:1 mixture of (214) and the desired pyrocatechol (215). However the allyl pyrocatechol (215) was easily separated from the eugenol (214) on a short silica column using chloroform as elutant. Thus use of more aluminium chloride or a more effective demethylating agent such as boron tribromide was considered not to be necessary. The allyl pyrocatechol (215) was then readily hydrogenated using a 10% palladium/carbon catalyst to give excellent yields (90%) of 4-n-propylpyrocatechol (216).



Scheme 98.

A sample of n-butylpyrocatechol (218) was prepared by Clemmensen reduction of the butyrylpyrocatechol (217) supplied by Prof. R.B. Cain (Scheme 99).

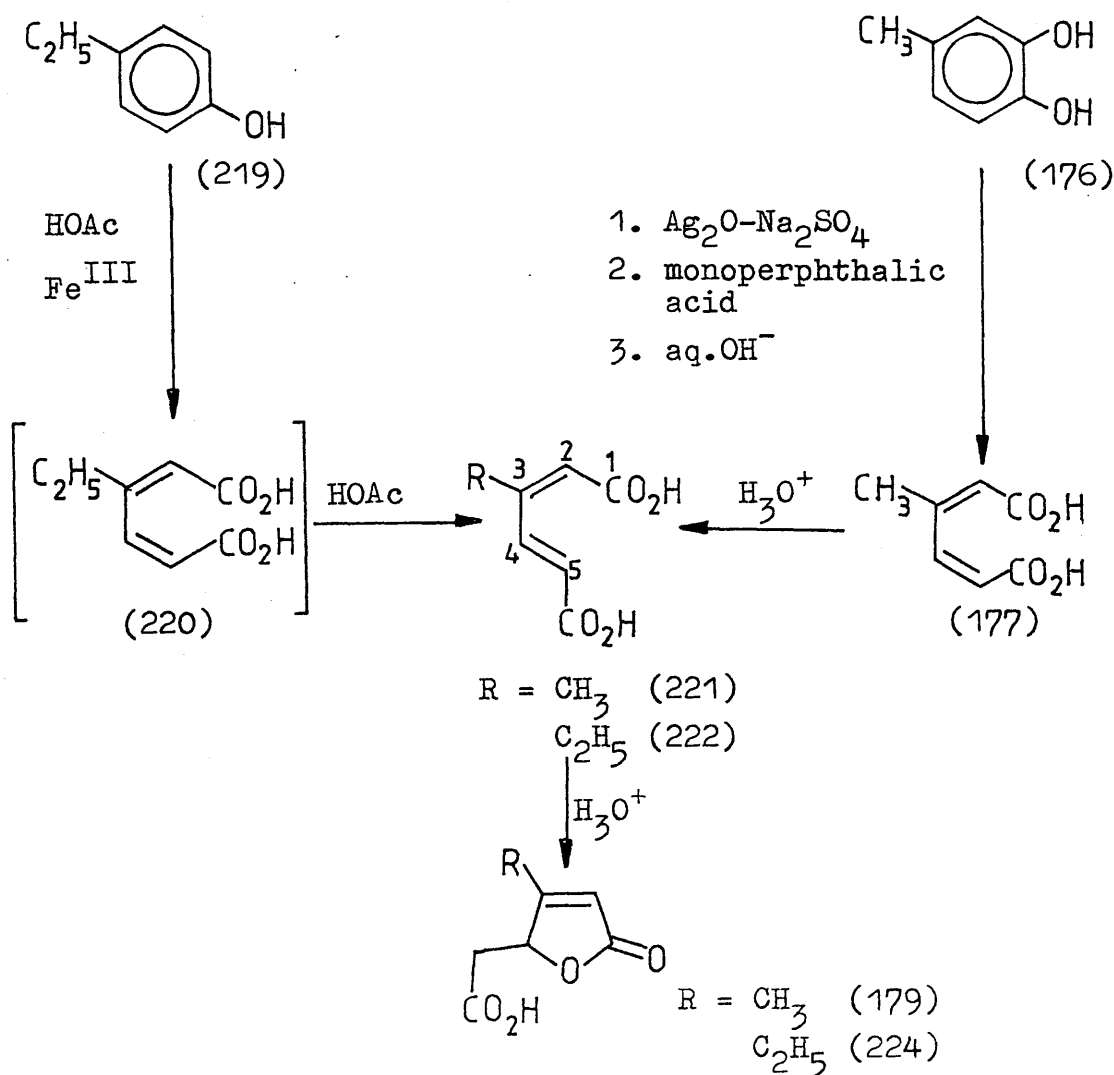


Scheme 99.

Preparation of (\pm)-3-ethylmuconolactone and the related dilactone.

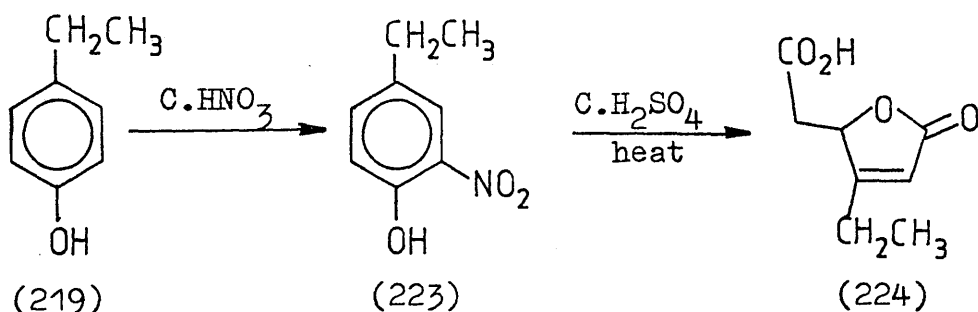
The first attempt at the preparation of (\pm)-3-ethylmuconolactone (224) involved acid catalysed cyclisation of the muconic acids (220)+(222) (Scheme 100). Thus 4-ethylphenol (219) was treated with 3 equivalents of peracetic acid in the presence of a catalytic amount of ferric acetate, according to the procedure of Pandell⁹¹, discussed earlier for the preparation of cis,cis-muconic acid (156). It was shown by 1H n.m.r. spectroscopy that the product which precipitated was, as expected, not the cis,cis-muconic acid (220), but instead the cis,trans isomer (222), formed by acid catalysed isomerisation of (220). Whereas the 1H n.m.r. spectrum for cis,cis-muconic acid (156) showed an AA'BB' system at δ 6.04 and 7.78 with a cis coupling constant $J_{2,3}=9Hz$, that of (222) showed an AB quartet at δ 6.18 and 8.37 with a trans coupling constant $J_{4,5}=14Hz$. Kirby et al.⁸⁴ did not prepare 3-methyl, 2-cis,4-trans-muconic acid (221) by direct cleavage of the methylpyrocatechol (176) but they found that (221) was formed rapidly even at pH 6.5 by isomerisation of

3-methyl cis,cis-muconic acid. The ^1H n.m.r. spectrum of (222) agreed closely, apart from necessary differences with that reported (Elvidge et al.⁹⁸) for (221). The acid (222), obtained in low yield (18%), was cyclised in dilute sulphuric acid to give (+)-3-ethylmuconolactone (224) as the sole product. Likewise, Elvidge et al.⁹² reported the corresponding cyclisation of (221) to give (+)-3-methylmuconolactone (179) (Scheme 100). The low yield of (222) may be due to the fact that some muconic acid is cyclising to the muconolactone in the acidic oxidation medium, although no muconolactone was in fact isolated.



Scheme 100.

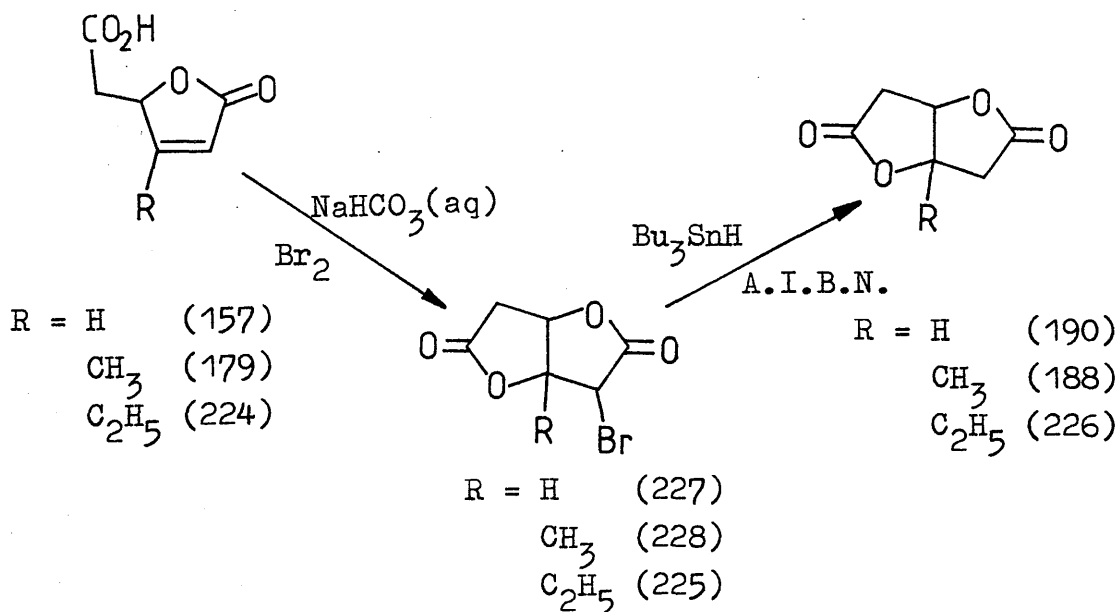
An alternative method which gave a better yield of the lactone (224), was a variation of that described by Pauly et al.⁹⁶. This involved preparation of (224) from 4-ethyl-2-nitrophenol (223) (Scheme 101). Since 4-ethylphenol (219) is activated towards electrophiles, nitration was carried out successfully using concentrated nitric acid alone, to give a dark mixture from which the desired product (223) was obtained in low yield (12%) by steam distillation. The nitrophenol (227) was added in portions to hot concentrated sulphuric acid at 110-115°C, during the course of 2h, to give a dark mixture from which the muconolactone (224) was obtained as cream crystals (65%). Attempted preparation of (224) using higher temperatures and shorter reaction times gave a solid black gel-like mass from which no product could be obtained.



Scheme 101.

Unlike the unsubstituted muconolactone but like 3-methylmuconolactone (179), 3-ethylmuconolactone (224) also could not be cyclised by acid catalysis to give the corresponding bicyclic dilactone (226). Instead,

(225) was synthesised by bromolactonisation. Treatment of the lactone (224) with sodium bicarbonate (aq) and bromine in dichloromethane gave the crystalline bromodilactone (225) in good yield (82%). This was then debrominated using tributyltinhydride with a catalytic amount of azo-bis-isobutyronitrile in benzene to give the dilactone (226) (Scheme 102). The yield reported by Elvidge *et al.*⁹² for the parent dilactone (190) was not reproduced. These authors produced (190) by cyclisation of the monolactone (157) in concentrated hydrochloric acid in moderate yield. In contrast we found that bromolactonisation to give (227) followed by reduction, by the methods discussed above, gave (190) in 85% yield.



Scheme 102.

In preliminary experiments⁹⁷, it was shown that the ethyldilactone (226) was slowly metabolised by cells of the isomerase enzyme from Rhodococcus ruber. The corresponding methyldilactone (188) and the parent dilactone (190) are good substrates for the isomerase enzyme.

Feeding Experiments with cultures of Pseudomonas putida.

Feeding of 4-ethylpyrocatechol (200).

The 4-ethylpyrocatechol (200) was then tested as a substrate for the enzymes of the bacterium Pseudomonas putida under the conditions employed successfully with the methyl derivative (176). Thus, 4-ethylpyrocatechol was fed, in three instalments to cultures of Ps. putida. After 30h, a ferric chloride test of the medium showed that there was negligible pyrocatechol left. At pH 7.5, the entire culture medium was extracted with ether and the ether extracts were analysed by ¹H n.m.r. spectroscopy. This showed that small amounts of unreacted 4-ethylpyrocatechol had been recovered. When the culture medium was again extracted with ether at pH 2.5 and the ether extracts analysed by ¹H n.m.r. spectroscopy, 4-ethylmuconolactone (229) was identified as the major product along with traces of 3-ethylmuconolactone (224). Similar observations were made when the feeding experiment was repeated on two later occasions. The results of the feeding experiments

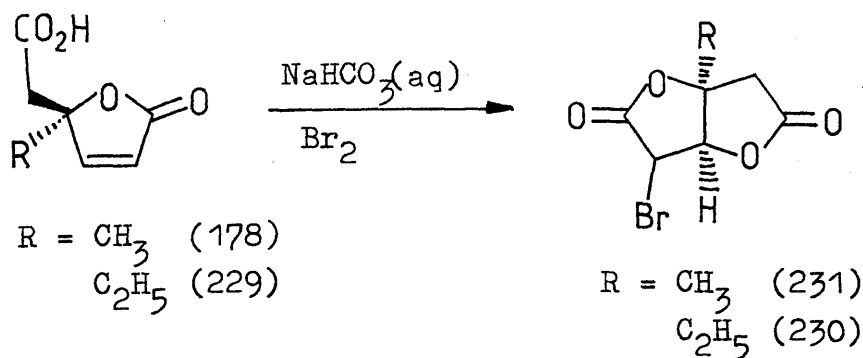
are shown in Table XII.

Table XII. Results of feeding 4-ethylpyrocatechol to cultures of Ps. putida.

Experiment	1	2	3
Amounts of pyrocatechol fed.	450mg	250mg	1g
incubation time	30h	30h	30h
yield of pyrocatechol (200) recovered	60mg (13%)	30mg (12%)	60mg (1%)
yield of lactone mixture (229)+(224)	160mg (30%)	60mg (22%)	80mg (7%)
proportion of (229):(224)	<u>ca.</u> 4:1	<u>ca.</u> 4:1	<u>ca.</u> 4:1

The 4-ethylmuconolactone (229) isolated was not crystalline. In order to determine its optical rotation, it was separated from the 3-ethylmuconolactone present on silica plates, using diisopropyl ether-formic acid-water (200:7:3) as elutant. Only the 4-ethylmuconolactone was recovered after chromatographic purification. The traces of 3-ethylmuconolactone were not recovered. The values measured for the optical rotation of the 4-ethylmuconolactone (38) were not consistent but they had the same sign, viz. $[\alpha]_D = +7.9$ (c, 0.95 in methanol) and + 19.7 (c, 0.88 in methanol).

(4S)-4-methylmuconolactone, isolated from Ps. putida has $[\alpha]_D = + 34.7$ (c, 1.32 in water). Thus, it seems highly probable that the configuration of the bacterial 4-ethylmuconolactone is also 4S. In an attempt to confirm this, it was decided to prepare the bromodilactone (230), for optical rotatory dispersion studies (Scheme 103). It was hoped that this would be crystalline and readily purified and would give a Cotton curve with the same sign as that produced by methylbromodilactone (231). Bromolactonisation gave a ca. 1:1 mixture of the bromodilactone (230) and unreacted 4-ethylmuconolactone (229). Attempts to separate this mixture on silica plates using ethyl acetate-hexane (2:1) as elutant, however, led to unexpected decomposition of the bromodilactone to give products which could not be identified.

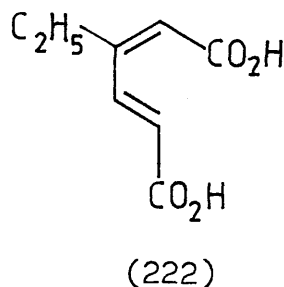
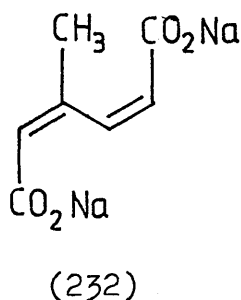


Scheme 103.

In the three experiments greater amounts of unreacted 4-ethylpyrocatechol (200) were recovered and smaller quantities of 4-ethylmuconolactone (229) were isolated than had been observed in the corresponding

methylmuconolactone feedings. This suggests that the bulkier ethyl group makes the pyrocatechol a poorer substrate for the dioxygenase enzyme. It may also affect the rate of enzymic cyclisation of the intermediate cis,cis-ethylmuconic acid. In the three experiments, similar amounts of the 3-ethylmuconolactone (224) were detected by ^1H n.m.r. spectroscopy (ca. 20% of the mixture by ^1H n.m.r. integration). Kirby et al.⁸⁵ found that ca. 8% of the lactone mixture isolated from the metabolism of 4-methylpyrocatechol was the 3-methylmuconolactone [racemate of (129)]. Presumably these 3-alkylmuconolactones must have arisen by non-enzymic cyclisation of the 3-methyl- and 3-ethylmuconic acids formed in vivo from the 4-methyl and 4-ethylpyrocatechols. Kirby et al.⁸⁵ were later to show that the disodium salt (232), when fed to cultures of Ps. putida, gave optically pure 4-methylmuconolactone accompanied by a greatly increased amount (77% of the mixture) of racemic 3-methylmuconolactone, thus supporting the proposed non-enzymic cyclisation. The fact that the proportion of 3-ethylmuconolactone in the total mixture, isolated in our experiments, was twice as much as the proportion of 3-methylmuconolactone in the total mixture observed by Kirby et al.⁸⁵, serves as further evidence that ethylpyrocatechol is a less acceptable substrate for the dioxygenase enzyme. It is also noteworthy that the non-enzymic cyclisation of the 3-ethyl-2-cis-4-trans-muconic acid (222), catalysed by acid, gave only racemic

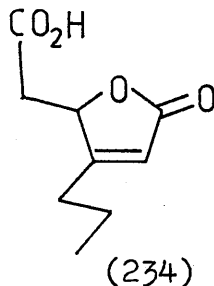
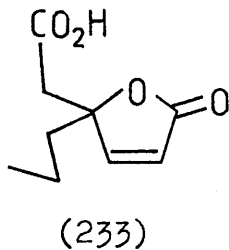
3-ethylmuconolactone. No 4-ethylmuconolactone was formed. Thus the 4-ethylmuconolactone formed, as discussed above, is almost certainly an enzymic product.



Feeding of 4-n-propylpyrocatechol (216).

In a similar manner, 4-n-propylpyrocatechol (216) (300mg) was fed to seven flasks of Ps. putida cultures. After 30h, the culture medium was extracted using ether at pH 7.8 and the extracts, analysed by ^1H n.m.r. spectroscopy, were shown to contain mainly the unmetabolised pyrocatechol (216) (180mg). When the culture medium was extracted at pH 2.5, the ^1H n.m.r. spectrum of the ether extracts showed traces of minor products giving, a multiplet at $\delta 5.15-5.30$, a broad singlet at $\delta 5.86$ and an AB quartet at $\delta 6.09$ and 7.56 . These may be due to the n-propylmuconolactones (233) and (234) although the very small amounts present could not be identified as such. It may be that the n-propylmuconolactones (233) and (234) can be obtained from feeding experiments carried out on a far greater

scale. The fact that the 4-n-propylpyrocatechol was largely recovered serves as further evidence that pyrocatechols with larger alkyl groups at the 4 position are poor substrates for the dioxygenase enzyme.



Feeding experiments with 4-n-butylpyrocatechol were not attempted.

3. Conclusions.

The biosynthetic experiments with Pseudomonas putida show that 4-substituted pyrocatechols with alkyl groups larger than methyl are not so readily cleaved by the dioxygenase enzyme which effects their conversion into the corresponding muconic acids. It may be that subsequent cyclisation to give 4-alkyl-muconolactones is also retarded by larger alkyl groups. The latter point could be tested by experiments with cis,cis-4-alkylmuconic acids synthesised⁹⁸ non-enzymically. Nevertheless, optically active 4-ethylmuconolactone (229) was produced directly from the corresponding pyrocatechol in cultures of Ps. putida. The fact that it was accompanied by substantial amounts of 3-ethylmuconolactone (224), presumed to be racemic, suggests that, indeed, the initial cis,cis-3-ethylmuconic acid (220) was a relatively poor substrate for the lactonising enzyme. The 4-ethyl- and 4-n-propylpyrocatechols are now available for testing as substrates for the fungus Aspergillus niger. Also, a feeding experiment with the 4-allylpyrocatechol (215) and Pseudomonas putida would be interesting. It would be expected that 4-ethylpyrocatechol would be converted in A. niger into (-)-3-ethylmuconolactone (224). However, this metabolite might be formed in partially racemic form owing to non-enzymic cyclisation of the intermediate cis,cis-3-ethylmuconic acid (220).

CHAPTER 3.

Experimental.

1. General Procedures.

M.p.s were recorded on a Kofler hot-stage apparatus and are uncorrected.

I.r. spectra were recorded on either a Perkin-Elmer 580 or 257 spectrometer by Mrs. F. Lawrie and her staff. All solid samples were prepared by dispersion in potassium bromide discs.

Proton n.m.r. spectra were recorded on a Perkin-Elmer R32 (90MHz) spectrometer, unless otherwise stated. 200MHz spectra were recorded on a Bruker W.P. 200SY instrument in the pulsed Fourier Transform (F.T.) mode by Mr. J. Gall. Unless otherwise stated, deuteriochloroform was used as the solvent with tetramethylsilane as internal standard. When D₂O was used as solvent, t-butanol (δ 1.28) was used as internal standard. All proton chemical shifts are quoted to the nearest 0.01 p.p.m.

Low resolution mass spectra were recorded in the E.I. mode at 70 eV on an A.E.I.M.S. 12 instrument, and high resolution spectra on an A.E.I.M.S. 9 instrument coupled to a GEC-905 computer for data collection and processing, by Mr. A. Ritchie and his staff. Microanalysis was performed by Mrs. K. Wilson.

Analytical t.l.c. was carried out on precoated Merck Kieselgel GF₂₅₄ plates of thickness 0.25mm. Spots were viewed under a u.v. lamp (254nm) and developed by iodine

vapour. Column chromatography was carried out on Merck silica HF₂₅₄ or 60H under reduced pressure according to the method of Harwood⁹⁹. Preparative t.l.c. was carried out on 20cm x 20cm glass plates coated with a 0.5mm layer of Merck GF₂₅₄ silica with detection of compounds by u.v. light.

All solvents and reagents were of analytical grade unless otherwise stated. 'Light petroleum' refers to the fraction of b.p. 60-80°C. 'Ether' refers to diethyl ether. Organic solvents were generally dried using magnesium sulphate and evaporated on a Buchi rotary evaporator under water-pump vacuum with slight heating.

2. Sulphines from Cyclopentadiene-thioaldehyde
cycloadduct S-Oxides Prepared by Oxidation of the
Corresponding Sulphides.

Preparation of Bunte salts and thiotosylates.

Sodium Phenacyl Thiosulphate (48).

This was prepared in 72% yield by the method of Milligan and Swan¹⁰⁰ from phenacyl bromide and sodium thiosulphate pentahydrate in aqueous ethanol; ν_{\max} . (KBr) 1670cm^{-1} . This value agrees well with that reported by Milligan and Swan¹⁰⁰.

Sodium 4-Bromophenacyl Thiosulphate (49).

This was likewise prepared in 70% yield; ν_{\max} . (KBr) 1673cm^{-1} ; $\delta_{\text{H}}(\text{D}_2\text{O})$ 4.58 (s, CH_2) and 7.54 and 7.81 (ABq, J 7Hz, ArH).

Sodium 4-Nitrobenzyl Thiosulphate (50).

This was prepared in 85% yield by the method of Price and Twiss¹⁰¹ from 4-nitrobenzyl bromide and sodium thiosulphate pentahydrate in aqueous ethanol; $\delta_{\text{H}}(\text{D}_2\text{O})$ 4.37(s, CH_2) and 7.61 and 8.09 (ABq, J 10Hz, ArH). The ^1H n.m.r. spectrum was essentially the same as that of a sample prepared by Sheldrake⁶⁴.

Sodium Cyanomethyl Thiosulphate (51).

This was prepared by Lohead's modification of the usual method¹⁰⁰ as follows:- Chloroacetonitrile (7.10g, 94 mmol) in ethanol (150ml) and sodium thiosulphate pentahydrate (23.36g, 94 mmol) in water (150ml) were heated under reflux for 3h. A homogeneous solution resulted and completion of the reaction was confirmed by analytical t.l.c. The solvents were evaporated and the white solid residue extracted with hot ethanol (120ml). The hot extracts were filtered. When the filtrate was cooled to 0°C, the Bunte salt (51) separated as white crystals (7.57g, 46%); $\nu_{\max.}(\text{KBr}) 2235\text{cm}^{-1}$. The i.r. spectrum was essentially the same as that of a sample prepared by Lohead¹⁰².

Sodium 4-Toluenethiosulphonate.

This was prepared in 70% yield by the method of Hayashi et al.¹⁰³ from 4-toluenesulphonyl chloride and sodium sulphide in aqueous ethanol.

S-Benzyl Toluene-4-thiosulphonate.

This was prepared in 80% yield by the method of Takano et al.¹⁰⁴ from sodium 4-toluenethiosulphonate, supported on an Amberlyst A26 resin, with benzyl bromide in boiling benzene; δ_{H} 2.43(s, CH₃), 4.27(s, CH₂), 7.15-7.35 (m, ArH) and 7.73(d, J, 7Hz, ArH). The ¹H n.m.r. spectrum agreed well with that reported by Takano¹⁰⁴.

Preparations of Thioaldehyde-cyclopentadiene adducts.

(1) Using Bunte salts as thioaldehyde precursors.

General Procedure⁵³.

Typically, the Bunte salt (20 mmol), cyclopentadiene (0.2ml, 24 mmol) in methanol (50ml) were cooled to 0°C. Triethylamine (3.3ml, 24 mmol) was added dropwise and the mixture was stirred at room temperature for 24h. The mixture was then acidified with dilute hydrochloric acid, to dissolve the precipitate of calcium sulphite, and was extracted into chloroform (50ml). The extract was washed successively with aqueous sodium bicarbonate (2 x 50ml) and water (50ml). The solution was dried and the solvent evaporated to give the crude product.

3-Benzoyl-2-thiabicyclo[2.2.1]hept-5-ene (52).

This was purified on a short silica column using chloroform as elutant to give the adducts (52) (64%) (endo:exo, 7:3), m.p. 88-90°C (lit.⁵³ 88-89°C); endo-adduct, δ_H 1.68(m, 7-CH₂), 3.80(m, 4-H), 4.09(m, 1-H), 5.12(d, J 4Hz, 3-H) 6.12(dd, J 5 and 2Hz, 5- or 6-H), 6.36(dd, J 5 and 2Hz, 6- or 5-H), 7.40-7.58(m, ArH) and 7.86-7.98(m, ArH); exo-adduct, δ_H 1.50-1.70(m, 7-CH₂), 3.66(m, 4-H), 4.30(s, 3-H), 4.12(m, 1-H) 6.05(dd, J 5 and 2Hz, 5- or 6-H), 6.43(dd, J 5 and 2Hz, 6- or 5-H), 7.40-7.55(m, ArH) and 7.86-7.97(m, ArH).

3-(4-Bromobenzoyl)-2-thiabicyclo[2.2.1]hept-5-ene (53).

This was likewise purified to give the adducts (53) (69%) (endo:exo, 8:3), m.p. 110-120°C (lit.⁵³ endo:108-110°C, exo:122-123°C); endo-adducts, δ_H 1.72(m,7-CH₂), 3.74(m,4-H), 4.07(m,1-H), 5.01(d,J 4Hz,3-H), 6.12(dd,J 5 and 2Hz, 5- or 6-H), 6.32(dd,J 5 and 2Hz, 6- or 5-H) and 7.54 and 7.75 (ABq,J 10Hz,ArH); exo-adduct, δ_H 1.73-2.00(m,7-CH₂), 3.60 (m,4-H), 3.96(s,3-H), 4.14(m,1-H), 6.07(dd,J 5 and 2Hz, 5- or 6-H), 6.67(dd,J 5 and 2Hz, 6- or 5-H) and 7.50 and 7.76(ABq,J 10Hz, ArH).

3-(4-Nitrophenyl)-2-thiabicyclo[2.2.1]hept-5-ene (54).

This was purified by crystallisation to give the adducts (54) (87%) (endo:exo, 7:1), m.p. 76-78°C (ethanol) (lit.⁵³ 76-78°C); endo-adduct, δ_H 1.77(m,7-CH₂), 3.60 (m,4-H), 4.20(m,1-H), 4.96(d,J 4Hz,3-H), 5.43(dd,J 6 and 3Hz, 5- or 6-H), 6.50(dd,J 6 and 3Hz, 6- or 5-H) and 7.40 and 8.05(ABq,J 10Hz,ArH); exo-adduct, δ_H 1.50-1.90 (m,7-CH₂), 3.27(m,4-H), 4.04(s,3-H), 4.25(m,1-H), 6.13 (dd,J 6 and 3Hz, 6- or 5-H), 6.44(dd,J 6 and 3Hz, 5- or 6-H) and 7.66 and 8.12(ABq,J 10Hz,ArH).

3-Cyano-2-thiabicyclo[2.2.1]hept-5-ene (55).

This was purified by Kugelrohr distillation, b.p. 90-95°C (0.02mmHg) (lit.⁵³ 90°C, 0.02mmHg) to give the adducts (55) (70%) (endo:exo, 2:1) as a clear liquid;

endo-adduct, δ_H 1.88(m,7-CH₂), 3.80(m,4-H), 4.32(m,1-H), 4.32(d,J 4Hz,3-H), 6.13(dd,J 6 and 3Hz, 5- or 6-H), 6.68 (dd,J 6 and 3Hz, 6- or 5-H); exo-adduct, δ_H 1.70-1.75 (m,7-CH₂), 3.28(s,3-H), 3.80(m,4-H), 4.32(m,1-H), 5.89 (dd,J 6 and 3Hz, 5- or 6-H) and 6.44(dd,J 6 and 3Hz, 6- or 5-H).

(2) Using α -sulphonyldisulphides as thioaldehyde precursors.

Benzyl Phenyl(toluene-4-sulphonyl)methyl Disulphide (88).

This was prepared (in 70% yield) by the method of Sheldrake⁶⁴ by addition of triethylemine to S-benzyltoluene-4-thiosulphonate in chloroform; m.p. 148-150°C (from ethanol) (lit.⁶⁴ m.p. 147.5-148.5°C); δ_H 2.37(s,CH₃), 2.92(s,CH₂), 4.63(s,CHSO₂) and 7.55-6.97(m,ArH).

3-Phenyl-2-thiabicyclo[2.2.1]hept-5-ene (84).

This was prepared in 55% yield by the method of Sheldrake⁶⁴ by addition of triethylamine to the foregoing α -sulphonyl disulphide (88) and cyclopentadiene in methanol-benzene (1:1) to give the adducts (84) (endo:exo, 8:3) which were purified by Kugelrohr distillation, b.p. 100-105°C (0.05mmHg) (lit.⁶⁴ 115°C, 0.03mmHg); δ_H 1.41-1.89(m,7-CH₂, both isomers), 3.21(m,4-H_{exo}), 3.52 (m,4-H_{endo}), 3.99(s,3-H_{exo}), 4.07(m,1-H_{endo}), 4.10 (m,1-H_{exo}), 4.38(d,J 4Hz,3-H_{endo}), 5.47(dd,J 5 and 2Hz, 5- or 6-H_{endo}), 6.02(dd,J 5 and 2Hz, 6- or 5-H_{exo}), 6.31 (dd,J 5 and 2Hz, 5- or 6-H_{exo}), 6.46(dd,J 5 and 2Hz, 6- or 5-H_{endo}) and 7.10-7.59(m,ArH).

The ^1H n.m.r. spectra of (52)-(55) and (84) were similar to those of samples prepared by Kirby et al.^{53,64}.

Chromatographic separation of endo and exo adducts.

Of the five cyclopentadiene thioaldehyde adducts, only the ketones, i.e. the 3-benzoyl-(52) and 3-(4-bromobenzoyl)-derivative(53), were separable, in these cases with silica plates developed three times in ether light petroleum (3:7). All others were inseparable by this method in this solvent system and in other solvent systems.

Thermodynamic Equilibration of the Thioaldehyde Cyclopentadiene Adducts.

General Procedure.

The thioaldehyde adduct (20 mmol) was heated under reflux in toluene (20ml) under nitrogen for the time indicated below. The reaction mixture was then cooled, the solvent evaporated and the adduct mixture analysed by ^1H n.m.r. spectroscopy. In preliminary experiments, each adduct was heated for successively longer periods until there was no change in the ^1H n.m.r. spectrum. The longest period employed is quoted below together with the final thermodynamic ratio of isomers.



<u>R(adduct)</u>	<u>Approximate equilibration time</u>	<u>Thermodynamic ratio</u> <u>endo:exo</u>
COPh (52)	5h	1:5
4-BrC ₆ H ₄ CO (53)	5h	1:5
4-NO ₂ C ₆ H ₄ (54)	2h	1:1
CN (55)	9h	1:1
Ph (84)		1:1

Preparation of Cyclopentadiene-thioaldehyde Cycloadduct
S-Oxides by Oxidation.

General Procedure

The corresponding sulphide (5 mmol) in dichloromethane (10ml) and 85% 3-chloroperbenzoic acid (1.01g, 5.88 mmol) also in dichloromethane (10ml) were mixed at 0°C. The resultant solution was stirred for about 1h after which time both starch-iodide paper and t.l.c. indicated that oxidation was complete. The reaction mixture was washed with sodium sulphite solution (20ml), sodium bicarbonate solution (2 x 20ml), and water (2 x 20ml), dried, and evaporated to give the crude S-oxide.

3-endo-Benzoyl-2-thiabicyclo[2.2.1]hept-5-ene
exo-S-Oxide (58).

The crude S-oxide was obtained as a yellow gum which crystallised after purification on a short silica column using ethyl acetate-light petroleum (3:7) as elutant. The sulphoxide (58) (0.93g, 80%) had m.p. 116-120°C (from toluene-hexane) (Found: m/z 232.2962. $C_{13}H_{12}O_2S$ requires M, 232.2971); ν_{\max} . (KBr) 1670 and 1025 cm^{-1} ; δ_H 2.30(dt, J 10 and 2Hz, 7-H), 2.67(d, J 10Hz, with fine splitting, 7-H), 3.45(m, 4-H), 4.23(d, J 4Hz, 3-H), 4.25(m, 1-H), 5.68(dd, J 6 and 3Hz, 5- or 6-H), 6.74(dd, J 6 and 3Hz, 6- or 5-H) and 7.35-7.55 and 7.95-8.10(2xm, ArH).

3-endo-(4-Bromobenzoyl)-2-thiabicyclo[2.2.1]hept-5-ene
exo-S-Oxide (59).

The crude S-oxide was obtained as a yellow gum which crystallised after purification on a short silica column using ethyl acetate-light petroleum (1:4) as elutant. The sulphoxide (59) (1.18g, 76%) had m.p. 153-156°C (from toluene-hexane) (Found: C 50.05; H 3.57; S 10.47; Br 25.54. $C_{13}H_{11}BrO_2S$ requires C, 50.17; H, 3.56; S, 10.37; Br 25.61%); ν_{\max} . (KBr) 1673, 1582 and 1048 cm^{-1} ; δ_H 2.37 (d, J 10 and 2Hz, 7-H), 2.73(d, J 10Hz, with fine splitting, 7-H), 3.51(m, 4-H), 4.25(d, J 4Hz, 3-H), 4.33 (m, 1-H), 5.76 (dd, J 6 and 3Hz, 5- or 6-H), 6.81(dd, J 6 and 3Hz, 6- or 5-H), and 7.67 and 7.96(ABq, J 9Hz, ArH).

3-exo-(4-Bromobenzoyl)-2-thiabicyclo[2.2.1]hept-5-ene
exo-S-Oxide (78).

The crude S-oxide was obtained as a brown gum. Attempted chromatography using either a silica column or a fluorosil column and ethyl acetate-light petroleum (1:4) as elutant, led to epimerisation, giving a mixture (66%) of both the above endo, exo, S-oxide(59) and the exo, exo, S-oxide(78) in varying proportions. (Found: m/z 310.2127 and 312.2067. $C_{13}H_{11}^{79}BrO_2S$ and $C_{13}H_{11}^{81}BrO_2S$ require M, 310.2109 and 312.2089); δ_H 2.38(dt, J 11 and 2Hz, 7-H), 2.97(d, J 11Hz, with fine splitting, 7-H), 3.62(m, 4-H), 4.26(m, 1-H), 4.36(s, 3-H), 5.97(dd, J 6 and 3Hz, 5- or 6-H), 6.43(dd, J 6 and 3Hz, 6- or 5-H) and 7.60 and 7.95(ABq, J 9Hz, ArH).

3-endo-(4-Nitrophenyl)-2-thiabicyclo[2.2.1]hept-5-ene
exo-S-Oxide (60).

The crude S-oxide was purified by recrystallisation from diethyl ether. The sulphoxide (60) (1.06g, 85%) had m.p. 108-110°C (from diethyl ether) (Found: C, 57.66; H, 4.40; N, 5.60; S, 12.68; m/z 249.1663. $C_{12}H_{11}NO_3S$ requires C, 57.82; H, 4.45; N, 5.61; S, 12.86% and M, 249.1642) ν_{max} . (KBr), 1578, 1342 and 1030 cm^{-1} ; δ_H 2.48(d, J 10 and 3Hz, 7-H), 2.86(d, J 10Hz, with fine splitting, 7-H), 3.48(m, 4-H), 3.91(d, J 4Hz, 3-H), 4.35 (m, 1-H), 6.08(dd, J 6 and 3Hz, 5- or 6-H), 6.25(dd, J 6 and 3Hz, 6- or 5-H) and 7.45 and 8.13 (ABq, J 9Hz, ArH).

3-endo-Cyano-2-thiabicyclo[2.2.1]hept-5-ene
exo-S-Oxide (61).

The crude S-oxide was obtained as brown gum which crystallised after purification on a short silica column using ethyl acetate-light petroleum (1:1) as elutant. The sulphoxide (61) (0.20g, 38%) had m.p. 58-60°C (from ethyl acetate-light petroleum) (Found: m/z 153.1971. C_7H_7NOS requires M, 153.1984); ν_{max} . 2235 and 1025 cm^{-1} ; δ_H 2.45(d, J 10 and 2Hz, 7-H), 2.79(d, J 10Hz, with fine splitting, 7-H), 3.11(d, J 4Hz, 3-H), 3.67(m, 4-H), 4.36 (m, 1-H), 6.04(dd, J 6 and 3Hz, 5- or 6-H) and 6.58 (dd, J 6 and 3Hz, 6- or 5-H).

Thermal 'Transfer' of Sulphines from Cyclopentadiene-thioaldehyde cycloadduct S-Oxides.

General Procedure.

The S-oxide (5 mmol) was heated with redistilled 2,3-dimethylbuta-1,3-diene (2.82ml, 25 mmol) in benzene (20ml) in a sealed tube under nitrogen for the appropriate time; A, 10h and B, 24h. Following cooling of the reaction mixture and evaporation of the solvent and the excess of diene, the crude product was obtained.

2-Benzoyl-4,5-dimethyl-6H-thiopyran (71) and 2-Benzoyl-3,6-dihydro-4,5-dimethyl-2H-thiopyran trans-S-Oxide (70a).
Reaction time A.

A brown gum was obtained upon thermolysis of the S-oxide (58) which, after purification on a short silica

column using light petroleum-ethyl acetate (1:9), gave unexpectedly, not the desired S-oxide (70a), but instead the thiopyran (71) (0.97g, 84%) as yellow crystals, m.p. 84-90°C (from toluene-light petroleum) (Found: m/z 230.3259. $C_{14}H_{14}OS$ requires M, 230.3246); ν_{\max} . (KBr) 1635cm^{-1} ; δ_H 1.67 and 1.71(2xs, 4- and 5-Me), 3.30(m, 6-H₂), 6.73(s, 3-H) and 7.40-7.60 and 7.86-8.02(2xm, ArH).

When rigorously purified trans-sulphoxide (58) was used, however, the trans-sulphoxide (70a) was isolated (72%), m.p. 122-124°C (lit.⁴¹ 122-127°C for trans + cis); δ_H 1.70 and 1.72(2xs, 4- and 5-Me), 2.64(m, 3-H₂), 3.47 (m, 6-H₂), 4.79(t, J 7Hz, 2-H) and 7.40-7.60 and 7.85-8.03 (2xm, ArH).

2-(4-Bromobenzoyl)-3,6-dihydro-4,5-dimethyl-2H-thiopyran trans-S-Oxide (67a). Reaction time A.

Upon thermolysis of the S-oxide (59), a yellow gum was obtained, which after purification on a short silica column using ethyl acetate-light petroleum (7:3) as elutant, gave the thiopyran (67a) as yellow crystals (1.24g, 76%), m.p. 104-110°C (from toluene-hexane) (Found: m/z 326.2551 and 328.2504. $C_{14}H_{15}^{79}\text{BrO}_2\text{S}$ and $C_{14}H_{15}^{81}\text{BrO}_2\text{S}$ require M, 326.2540 and 328.2520); ν_{\max} . (KBr) 1640 and 1070cm^{-1} ; δ_H (200mHz) 1.72 and 1.76 (2xs, 4- and 5-Me), 2.65(d, J 7Hz, 3-H₂), 3.54(m, 6-H₂), 4.73(t, J 7Hz, 2-H) and 7.63 and 7.88 (ABq, J 9Hz, ArH).

2-(4-Nitrophenyl)-3,6-dihydro-4,5-dimethyl-2H-thiopyran
trans-S-Oxide (68a). Reaction time A.

Upon thermolysis of the S-oxide (60), a brown gum was obtained, which after purification on a short silica column using ethyl acetate-light petroleum (3:2) as elutant, gave the thiopyran (68a) as sand coloured crystals (1.22g, 92%), m.p. 131-133°C (from diethyl ether) (Found: C, 58.81; H, 5.65; N, 5.04; S, 11.88; m/z 265.3252. $C_{13}H_{15}NO_3S$ requires C, 58.84; H, 5.69; N, 5.27; S, 12.07% and M, 265.3270); ν_{\max} . (KBr) 1518, 1342 and 1040cm^{-1} ; δ_H 1.69(2xs, 4- and 5-Me), 2.18(m, 3-H₂), 3.38(m, 6-H₂), 4.11(dd, J 6 and 9Hz, 2-H) and 7.45 and 8.10(ABq), J 9Hz, ArH).

2-Cyano-3,6-dihydro-4,5-dimethyl-2H-thiopyran trans-
S-Oxide (69a). Reaction time B.

Upon thermolysis of the S-oxide (61) a brown oil was obtained, which after purification by Kugelrohr distillation, b.p. 122-127°C gave the thiopyran (69a) as a clear oil (0.52g, 62%) (Found: m/z 169.2497, $C_8H_{11}NOS$ requires M, 169.2470); ν_{\max} . (thin film) 2240 and 1060cm^{-1} ; δ_H 1.68 and 1.70(2xs, 4- and 5-Me), 2.92(m, 3-H₂), 3.54(m, 6-H₂) and 3.98(t, J 7Hz, 2-H).

Reactions To Confirm S-Oxide Stereochemistry.

Cyclopentadiene-thioaldehyde Adduct S-Oxides.

Base-induced Epimerisation of trans-S-Oxides.

The 3-(4-bromobenzoyl) trans-S-oxide (59) and triethylamine (1 mol equiv.) were heated in toluene (20ml) at 60°C for 6h. The mixture was cooled, washed with dilute hydrochloric acid (20ml) and water (20ml), then it was dried. The solvent was evaporated and the residue analysed by n.m.r. spectroscopy. This showed the trans-S-oxide (59) with only traces of the cis-S-oxide (78).

Epimerisation of the 3-(4-bromobenzoyl) cis-S-Oxide (78).

Attempted chromatographic purification of the cis-S-oxide (78) on silica or fluorosil using ethyl acetate-light petroleum (1:4) invariably led to rapid epimerisation at room temperature to give cis(78) trans(59) S-oxide mixtures in varying proportions; viz. cis:trans 2:1 and 1:1 on different occasions. In contrast, the 3-(4-bromobenzoyl) trans-S-oxide (59) was purified on at least two occasions using the same conditions and was obtained pure with no traces of the cis-S-oxide (78).

2,3-Dimethylbuta-1,3-diene-thioaldehyde Adduct S-Oxides.

Preparation of 2,3-Dimethylbuta-1,3-diene Thioaldehyde Adducts.

The method of Kirby et al.⁵³ was used to prepare the sulphides (74), (76) and (77) by addition of triethylamine (1.2 mol equiv.) in benzene to the appropriate Bunte salt in ethanol and benzene, containing the diene (3 mol equiv.) and calcium chloride dihydrate (1 mol equiv.). The mixtures were then refluxed for 4h and worked up as described⁵³ to give:-

2-benzoyl-3,6-dihydro-4,5-dimethyl-2H-thiopyran (74) (54%);

δ_H 1.73(2xs, 4- and 5-CH₃), 2.51(m, 3-H₂), 3.02(m, 6-H₂), 4.48(t, J 7Hz, 2-H) and 7.42-7.56 and 7.92-8.04(2xm, ArH).

2-(4-nitrophenyl)-3,6-dihydro-4,5-dimethyl-2H-thiopyran (76) (60%), m.p. 64-66°C (lit.⁵³ 64-64.5°C); δ_H 1.73 (2xs, 4- and 5-CH₃), 2.51(m, 3-H₂), 2.89 and 3.49(ABq, J 16Hz, 6-H₂), 4.07(t, J 7Hz, 2-H) and 7.46 and 8.15 (ABq, J 10Hz, ArH).

2-Cyano-3,6-dihydro-4,5-dimethyl-2H-thiopyran (77) (52%); δ_H 1.72 and 1.75(2xs, 4- and 5-CH₃), 2.52(m, 3-H₂), 2.94 and 3.54 (ABq, J 16Hz, 6-H₂) and 3.78(t, J 7Hz, 2-H).

The ¹H n.m.r. spectra for (74), (76) and (77) agreed well with those of samples prepared by Kirby et al.⁵³.

2-Ethyl-3,6-dihydro-4,5-dimethyl-2H-thiopyran (126).

This was prepared by the method of Baldwin and Lopez⁶⁶. Thus, S-propyl propanethiosulphinate (prepared by the method described on p.138)(0.83g, 5mmol)

and 2,3-dimethylbuta-1,3-diene (1.64g, 20 mmol) in dry toluene (10ml) were sealed in a tube and stirred and heated at 95-97°C for 24h. Evaporation and purification on a silica column using light petroleum-benzene (9:1) as elutant gave the adduct (126) (523mg, 83%) as a colourless oil. (Found: m/z 156.2889, $C_9H_{16}S$ requires M , 156.2919); ν_{max} . (thin film) 1455 and 752 cm^{-1} ; δ_H (CCl_4) 1.02 (t, J 7Hz, CH_2CH_3), 1.48(q, J 7Hz, with fine splitting, CH_2CH_3), 1.65(s, 4- and 5- CH_3) and 1.93-2.29 and 2.48-3.15(2xm, 2-H and 3- and 6- H_2).

Oxidation of the thioaldehyde adducts (74), (76) and (77) to give the S-Oxides (68), (69) and (70).

These were prepared by the general oxidation method described on p.128.

2-benzoyl-3,6-dihydro-4,5-dimethyl-2H-thiopyran cis-S-oxide (70b).

Oxidation of the sulphide (74) gave a cis:trans (ca. 1:4) S-oxide mixture, m.p. 120-124°C (lit.⁴¹ 122-127°C). The cis-oxide (70b) gave δ_H 1.72(s, 4- and 5- CH_3), 2.10-3.20(m, 3- H_2), 3.40(m, 6- H_2), 4.42(dd, J 4 and 10Hz, 2-H), and 7.44-7.60 and 7.86-7.97(2xm, ArH). Signals for the trans-oxide (70a) corresponded with those reported before for the sulphine adduct.

2-(4-Nitrophenyl)-3,6-dihydro-4,5-dimethyl-2H-thiopyran cis-S-Oxide (68b).

Oxidation of the sulphide (76) gave a cis:trans

(ca. 1:4) S-oxide mixture. The cis-isomer (68b) gave δ_H 1.70(s, 4- and 5-CH₃), 2.40-3.40(m, 3- and 6-H₂), 3.96(dd, J 4 and 10Hz, 2-H), and 7.51 and 8.19(ABq, J 10Hz, ArH). The trans isomer (68a) gave signals corresponding with those reported before for the sulphine adduct.

2-Cyano-3,6-dihydro-4,5-dimethyl-2H-thiopyran cis S-Oxide (69b).

Oxidation of the sulphide (77) gave a cis:trans (ca. 1:2) S-oxide mixture. The cis-isomer (69b) gave δ_H 1.69(s, 4- and 5-CH₃), 2.30-3.40(m, 3- and 6-H₂) and 3.72(dd, J 4 and 10Hz, 2-H). The trans isomer (69a) gave signals corresponding with those reported before for the sulphine adduct.

Base Induced Epimerisation of the Oxidation Mixtures.

Typically, the oxidation mixture (ca. 2 mmol) and triethylamine (2 mmol) in toluene (20ml) were stirred at room temperature for 6h. The mixture was then washed with dilute hydrochloric acid (20ml), water (20ml), then dried. The solvent was evaporated and the residue analysed by n.m.r. spectroscopy.

The 2-cyano and 2-benzoyl S-oxide mixtures (69) and (70) were recovered unchanged, i.e. cis:trans (1:4).

The 2-(4-nitrophenyl) S-oxide mixture (68) however had epimerised to give only the trans-S-oxide (68a).

3. Sulphines from Anthracene-thioaldehyde Cycloadduct S-Oxides Prepared by Oxidation of the Corresponding Sulphides.

Preparation of Disulphides and Alkyl Thiosulphinates.

All disulphides were prepared by one of two methods:-

Method A - Iodine Oxidation of Thiols.

Preparation of Dipropyl Disulphide (112).

Sodium hydroxide (1.04g, 26 mmol) and a small amount of potassium iodide were added to water (20ml) and swirled to effect complete dissolution. Ethanol (20ml) was added followed by 1-propanethiol (2.72ml, 0.03 mol). Iodine (1.90g, 0.015 mol) was then added in portions with shaking, ensuring each time that the solution became clear before further additions of iodine. Eventually, after all the iodine had been added and the solution had remained standing for a short time a pale yellow colour developed due to a slight excess of iodine which was discharged by addition of a further drop of thiol and swirling. Water (100ml) was added and the disulphide (112) extracted with dichloromethane (2 x 30ml). The extract was dried and evaporated to give the product as a yellow oil. After purification on a short silica column using petrol-dichloromethane (4:1), the disulphide (2.1g, 54%) was obtained as a pale yellow oil; δ_{H} (CCl_4), 1.00(t, J 7Hz, CH_2CH_3), 1.68(q, J 7Hz, CH_2CH_3) and 2.59(t, J 7Hz, SCH_2).

Method B - Iodine Oxidation of Bunte Salts.

A variation of the method of Price and Twiss¹⁰⁵ was used as follows:-

General Procedure.

The alkyl bromide or chloride (0.04 mol) was added to sodium thiosulphate pentahydrate (10g, 0.02 mol) in water (20ml) and ethanol (20ml) and the resulting solution was heated under reflux for 15 min. Iodine (5g, 0.02 mol) was then added in portions to the solution, which was kept hot, ensuring that it became clear after each addition. After 1-2h the solution had become colourless and was then cooled. In the case of solid disulphides, the crude disulphide separated as an oil which solidified and was crystallised from ethanol. In this way, the following disulphides were prepared:-

Dibenzyl disulphide (7.6g, 77%), m.p. 58-60°C (lit.¹⁰⁶ 59-60°C); δ_H 3.6(s, SCH₂) and 7.27(s, ArH).

Di-(4-nitrobenzyl)disulphide (96) (9.43g, 72%), m.p. 124-126°C (lit.¹⁰⁷ 126.5°C); δ_H 3.7(s, CH₂Ar) and 7.37 and 8.16(ABq, J 9Hz, ArH).

Di-(4-bromophenacyl)disulphide (107) (11.8g, 66%), m.p. 134-138°C; δ_H 4.11(s, CH₂Ar) and 7.56 and 7.77(ABq, J 10Hz, ArH).

In the case of the liquid disulphide, di-(cyanomethyl) disulphide (98) however, the cooled mixture was diluted

with water (40ml) and extracted with ether (3x15ml). The disulphide was obtained as a dark oil, which was purified using a short silica column with chloroform as elutant, followed by Kugelrohr distillation, b.p. 150°C (0.02mmHg), to give the disulphide (2.07g, 37%) as a clear oil.

All alkyl thiosulphinates were prepared by direct peracid oxidation of the corresponding disulphides, as described on p.128.

In this way, the following alkyl thiosulphinates were prepared:-

S-Propyl Propanethiosulphinate (113) (77%) b.p. 25-35°C (0.1mmHg).

S-Benzyl Phenylmethanethiosulphinate (80%), m.p.65-67°C; δ_H 4.26(s, SCH₂), 4.29(s, SOCH₂) and 7.30 and 7.35 (2xs, ArH).

S-4-Nitrobenzyl 4-Nitrophenylmethanethiosulphinate (105) (65%) m.p. 70-72°C (Found: C, 47.69; H, 3.38; N, 7.96; S, 18.29. C₁₄H₁₂N₂O₅S₂ requires C, 47.72; H, 3.43; N, 7.95; S, 18.20%); ν_{max} . (CHCl₃) 1524, 1349 and 1017cm⁻¹; δ_H 4.27(s, SCH₂), 4.41(s, SOCH₂) and 7.50 and 8.22 (ABq, J 9Hz, ArH).

S-4-Bromophenacyl 4-Bromobenzoylmethanethiosulphinate (108) (67%) m.p. 110-112°C; (Found: m/z 474.2392 and 478.2345. C₁₆H₁₂⁷⁹Br₂O₃S₂ and C₁₆H₁₂⁸¹Br₂O₃S₂ require M , 474.2337 and 478.2337); ν_{max} . (CHCl₃) 1670, 1585 and 1070cm⁻¹; δ_H (CD₃SOCD₃) 4.18(s, SCH₂), 4.35(s, SOCH₂) and 7.62-7.98 (m, ArH).

Preparation of Anthracene-Thioaldehyde Cycloadducts.

(1) 9,10-Dihydro-9,10-(2-ethyl-1-thiaethano)anthracene(114).

In a modification to the method of Baldwin and Lopez⁶⁶, S-propyl propanethiosulphinate (0.83g, 5 mmol) and anthracene (8.9g, 50 mmol) in dry toluene (75ml) were sealed in a tube and stirred and heated at 105°C for 14h^a. Cooling precipitated anthracene as white flakes which were filtered off. The filtrate was evaporated and the product separated from anthracene and other minor products on a silica column using light petroleum-benzene^b (7:3) as elutant. Recrystallisation (toluene-hexane) gave the adduct (114) as white crystals (0.98g, 77%) m.p. 137-139°C (Found: C, 80.93; H, 6.50; S, 12.53; calc. for C₁₇H₁₆S: C, 80.90; H, 6.39; S, 12.70%); ν_{\max} . (KBr) 3070-2840, 1470 and 1455cm⁻¹; δ_{H} 0.91(t, J 7Hz, CH₂CH₃), 1.93-2.68(m, CH₃CH₂), 3.25(m, 12-H), 4.47(d, J 3Hz, 10-H), 4.98(s, 9-H) and 7.03-7.35(m, ArH).

(2) All Other Adducts.

General Procedure.

The alkyl thiosulphinate (1 mmol) and anthracene (1.78g, 10.0 mmol) were stirred and heated in dry toluene (15ml) at 98-100°C under nitrogen for the times indicated below^a. After this, the solution was cooled to room temperature and left in the refrigerator overnight to precipitate out any unreacted anthracene, which was filtered off. The filtrate was evaporated and the

residual solid separated on a silica column using the solvent system described below^b to give the adduct along with unidentified minor impurities (and in one case a substantial amount of the disulphide^c). The adducts were recrystallised from toluene-hexane.

Table XIII. Experimental data for the preparation of anthracene-thioaldehyde adducts.

R(cycloadduct)	Reaction time ^a	Solvent system ^b
CH ₂ CH ₃ (114)	14h	light petroleum-benzene (7:3)
C ₆ H ₅ (104)	1h	light petroleum-benzene (7:3)
4-NO ₂ C ₆ H ₄ (100)		light petroleum-CH ₂ Cl ₂ (2:1)
4-BrC ₆ H ₄ CO (109)	2h	light petroleum-CH ₂ Cl ₂ (1:1)

9,10-Dihydro-9,10-(2-phenyl-1-thiaethano)anthracene (104).
(98%), m.p. 158-162°C (lit.⁶⁵ 160-163°C).

9,10-Dihydro-9,10-[2-(4-nitrophenyl)-1-thiaethano]-anthracene (100). (0.33g, 96%), m.p. 124-128°C (Found: $\underline{m/z}$ 345.4167. C₂₁H₁₅NO₂S requires \underline{M} , 345.4187); $\nu_{\text{max.}}$ (KBr) 1518 and 1347cm⁻¹; δ_{H} 4.48(d, \underline{J} 3Hz, 12-H), 4.61(d, \underline{J} 3Hz, 10-H), 5.24(s, 9-H), 6.9-7.45(m, ArH) and 6.86 and 7.93 (ABq, \underline{J} 10Hz, ArH).

9,10-Dihydro-9,10-[2-(4-bromobenzoyl)-1-thiaethano]-anthracene (109). (0.22g, 55%) along with (0.05g, 14%) of (96)^c. The adduct (109) had m.p. 120-124°C (Found:

m/z 406.3472 and 408.3441. $C_{22}H_{15}^{79}BrOS$ and $C_{22}H_{15}^{81}BrOS$ require M , 406.3455 and 408.3435); $\nu_{max.}$ (KBr) 1685, 1665 and $1584cm^{-1}$; δ_H 4.58(d, J 3Hz, 12-H), 5.08(d, J 3Hz, 10-H), 5.10(s, 9-H) and 7.1-7.65 (m, ArH).

Preparation of Anthracene-thioaldehyde Cycloadduct S-Oxides by Oxidation.

Oxidation of the adducts (100), (104), (109) and (114) using the procedure described on p.128 gave the following:-

9,10-Dihydro-9,10-(2-ethyl-1-thiaethano)anthracene

S-Oxide (122). (80%), m.p. $115-125^{\circ}C$ (cis + trans) (Found: m/z 268.3527. $C_{17}H_{16}OS$ requires M , 268.3509); $\nu_{max.}$ (KBr) 1670, 1452 and $1035cm^{-1}$; δ_H 1.15(t, J 7Hz, CH_2CH_3), 1.2-1.65(m, CH_2CH_3), 2.22(m, 12-H_{trans}), 2.86 (m, 12-H_{cis}), 4.39(d, J 3Hz, 10-H_{trans}), 4.54(d, J 3Hz, 10-H_{cis}), 5.60(s, 9-H_{trans}), 5.67(s, 9-H_{cis}) and 7.19-7.46(m, ArH).

9,10-Dihydro-9,10-(2-phenyl-1-thiaethano)anthracene

Trans-S-Oxide (120a). (94%), m.p. $145-147^{\circ}C$ (Found: C, 79.84; H, 5.14; S, 10.17. $C_{21}H_{16}OS$ requires C, 79.71; H, 5.10; S, 10.13%); $\nu_{max.}$ (KBr) 3027, 1450 and $1028cm^{-1}$; δ_H 3.42(d, J 3Hz, 12-H), 4.47(d, J 3Hz, 10-H), 5.69(s, 9-H), and 6.5-6.63 and 6.95-7.61(2xm, ArH).

9,10-Dihydro-9,10-[2-(4-nitrophenyl)-1-thiaethano]-anthracene Trans-S-Oxide (119a). (92%), m.p. 108-112°C (Found: C, 69.85; H, 4.16; N, 3.92; S, 8.79. $C_{21}H_{15}NO_3S$ requires C, 69.79; H, 4.18; N, 3.87; S, 8.87%); ν_{\max} . (KBr), 1516, 1362 and 1625 cm^{-1} ; δ_H 3.53(d, \underline{J} 3Hz, 12-H), 4.48(d, \underline{J} 3Hz, 10-H), 4.77(s, 9-H), 7.10-7.65(m, ArH) and 6.66 and 7.96(ABq, \underline{J} 10Hz, ArH).

9,10-Dihydro-9,10-[2-(4-bromobenzoyl)-1-thiaethano]-anthracene Trans-S-Oxide (121a) (82%) (Found: C, 62.35; H, 3.62; S, 7.61; Br, 18.71. $C_{22}H_{15}BrO_2S$ requires C, 62.42; H, 3.57; S, 7.52; Br, 18.87%); ν_{\max} . (KBr) 1680, 1665 and 1030 cm^{-1} ; δ_H 3.78(d, \underline{J} 3Hz, 12-H), 4.87(d, \underline{J} 3Hz, 10-H), 5.70(s, 9-H), 7.19-7.87(m, ArH).

Thermal 'Transfer' Experiments.

(1) Thermal 'Transfer' of Thioaldehydes using Anthracene Adducts.

General Procedure.

The anthracene adduct (5 mmol) was heated with redistilled 2,3-dimethylbuta-1,3-diene (2.82ml, 25 mmol) in refluxing toluene (10ml) under nitrogen, for the appropriate time (Table XIV). Following cooling and evaporation of the solvent and the excess of diene, the crude product was obtained along with anthracene and was analysed by 1H n.m.r. spectroscopy.

The 4-nitrophenyl derivative (100) gave (76)

(1.06g, 85%) having a ^1H n.m.r. spectrum identical to that found by Sheldrake⁶³. See also the preparation of (76) described above.

The 4-bromobenzoyl derivative (109) gave (75) (1.17g, 77%); δ_{H} 1.73(2xs, 4- and 5- CH_3), 2.48(m, 3-H), 2.97(m, 6-H), 4.42(t, $\underline{\text{J}}$ 7Hz, 2-H) and 7.57 and 7.86 (ABq, $\underline{\text{J}}$ 9Hz, ArH). A sample of (75) synthesised by the method of Kirby et al.⁵³, the procedure for which is outlined on p.135 gave identical n.m.r. signals. For this latter synthetic sample of (75) (Found: $\underline{\text{m/z}}$ 310.2559 and 312.2572. $\text{C}_{14}\text{H}_{15}^{79}\text{BrOS}$ and $\text{C}_{14}\text{H}_{15}^{81}\text{BrOS}$ require $\underline{\text{M}}$, 310.2573 and 312.2553); ν_{max} . (KBr) 1642cm^{-1} .

The phenyl derivative (104) gave (123) (0.85g, 83%) having a ^1H n.m.r. spectrum identical to that reported by Baldwin and Lopez⁶⁵; δ_{H} 1.73(2xs, 4- and 5- CH_3), 2.45 and 2.60(2xm, 3- H_2), 2.93 and 3.46(2xm, 6- H_2), 3.98(dd, $\underline{\text{J}}$ 6 and 9Hz, 2-H) and 7.25-7.38(m, ArH).

The ethyl derivative (114) was recovered unchanged after 48h heating.

Table XIV. Approximate 'transfer' times at ca. 111°C for thioaldehydes (RCHS) from anthracene adducts to give dihydrothiopyrans.

R(cycloadduct)	Approx. time for transfer
CH_2CH_3 (114)	no transfer after 48h
C_6H_5 (104)	1h
4- $\text{NO}_2\text{C}_6\text{H}_4$ (109)	15 min
4- $\text{BrC}_6\text{H}_4\text{CO}$ (109)	2h

(2) Thermal 'Transfer' of Sulphines from Anthracene-thioaldehyde Cycloadduct S-Oxides.

General Procedure.

The S-oxide (5 mmol) was heated with redistilled 2,3-dimethylbuta-1,3-diene (2.82ml, 25 mmol) in toluene (20ml) under nitrogen at 60°C (using a fixed temperature bath) for the times indicated in Table XV. Following cooling and evaporation of the solvent and the excess of diene, the crude product was obtained along with anthracene and analysed by ^1H n.m.r. spectroscopy.

The phenyl derivative (120a) gave (45a) giving δ_{H} 1.72(2xs, 4- and 5-CH₃), 2.73(m, 3-H), 3.29(m, 6-H), 4.09(dd, J 7 and 9Hz, 2-H) and 7.15(s, ArH). Bonini et al.¹⁷ reported δ 4.12(2-H).

The 4-nitrophenyl derivative (119a) gave (68a) (1.08g, 82%) having a ^1H n.m.r. spectrum identical to that described on p.133.

The 4-bromobenzyl derivative (121a) gave (67a) (1.12g, 68%) having a ^1H n.m.r. spectrum identical to that described on p.132.

The ethyl derivative (122) did not react in toluene, but in o-dichlorobenzene at 140°C both the cis and trans isomers (122a) and (122b) reacted as a mixture to give a mixture of the butadiene adducts (127a) and (127b) respectively (Found: m/z 172.2894. C₉H₁₆OS requires M, 172.2913); ν_{max} . (KBr) 1455 and 1070cm⁻¹; δ_{H} (CCl₄) 1.02(t, J 7Hz, CH₂CH₃), 1.60-2.10(m, CH₂CH₃), 1.66(s, 2xCH₃) and 2.15-2.35(m, 2-3- and 6-H). A sample of a mixture

synthesised by oxidation of the sulphide (126) also gave these signals.

Table XV. Approximate 'transfer' times at 60°C for sulphines from anthracene cycloadducts to give dihydrothiopyran S-oxides.

R(cycloadducts)	Approx. time for transfer
CH ₂ CH ₃ (122)	24h *
C ₆ H ₅ (120a)	2-3h
4-NO ₂ C ₆ H ₄ (119a)	1-2h
4-BrC ₆ H ₄ CO (121a)	4-5h

* At ca. 140°C in o-C₆H₄Cl₂

4. Sulphines from Thebaine-thioaldehyde Cycloadduct S-Oxides Prepared by Oxidation of the Corresponding Sulphides.

Preparation of the cycloadducts (136) and (137) of thebaine (106) and 4-nitrobenzaldehyde.

These were prepared according to the method of Sheldrake⁶⁴ by addition of triethylamine to the Bunte salt (50), thebaine (106), and calcium chloride dihydrate (all 1 mol equiv.) in ethanol-benzene (1:3). The mixture was stirred at room temperature for 18h , then worked up as described by Sheldrake⁶⁴ to give a mixture of the adducts (136) (34%) and (137) (33%) which were separated on a short silica column using

chloroform as elutant. When the same experiment was repeated, with a reaction time of 5d instead of 18h, the 7-thia adduct (136) was formed exclusively (1.06g, 56%), m.p. 195-197°C (from ethanol) (lit.⁶⁴ 195-196°C); δ_{H} 2.37(s, N-CH₃), 3.68(s, 6-OCH₃), 3.81(s, 3-OCH₃), 5.08(d, J 2Hz, 5-H), 5.18(d, J 9Hz, 19-H), 5.80(s, 8-H), 6.37(dd, J 2 and 9Hz, 18-H), 6.50 and 6.62 (ABq, J 8Hz, ArH) and 7.53 and 8.08(ABq, J 9Hz, ArH). The ¹H n.m.r. spectrum was essentially the same as that of a sample prepared by Sheldrake⁶⁴.

Preparation of the S-Oxide (134).

This was prepared from the foregoing 7-thia cycloadduct (136) by the general oxidation method as described on p.128. The sulfoxide (134) (0.15g, 88%) had m.p. 171-173°C (from ether) (Found: m/z 494.6372; C, 63.39; H, 5.31; N, 5.66; S, 6.29. C₂₆H₂₆N₂O₆S requires M, 494.6359; C, 63.13; H, 5.30; N, 5.66; S, 6.48%); $\nu_{\text{max.}}$ (KBr) 1520, 1350 and 1049cm⁻¹; δ_{H} (200 MHz) 2.21(s, N-CH₃), 3.82(s, 6-OCH₃), 3.90(s, 3-OCH₃), 5.13(s, 8-H), 5.58(d, J 9.1Hz, 19-H), 5.64(d, J 1.6Hz, 5-H), 5.99(dd, J 9.1 and 1.6Hz, 18-H), 6.52 and 6.63(ABq, J 8.2Hz, ArH) and 7.45 and 8.13 (ABq, J 8.9Hz, ArH).

Thermal 'Transfer' Experiments with Thebaine and the Anthracene Sulphine Adduct (119a) and Dimethylbutadiene and the Thebaine Sulphine Adduct (134).

Formation of the thebaine sulphine adduct (134) from the anthracene sulphine adduct (119a).

The sulfoxide (119a) (1.80g, 5 mmol) was heated with thebaine (1.56g, 5 mmol) in toluene (30ml) under nitrogen at 60°C (using a fixed temperature bath). The reaction was shown by t.l.c. to be complete after 2h. The reaction mixture was cooled and evaporated and the residue was analysed by ^1H n.m.r. spectroscopy. This showed that the sulfoxide (134) (1.90g, 77%) had been formed along with anthracene. The mixture was not further purified.

Formation of the dimethylbutadiene sulphine adduct (68a) from the thebaine sulphine adduct (134).

The sulfoxide (134) (1.48g, 3 mmol) was heated with 2,3-dimethylbuta 1,3-diene (15 mmol) in toluene (20ml) at 70°C (using a fixed temperature bath). After 24h, the reaction mixture was cooled and evaporated and the residue was analysed by ^1H n.m.r. spectroscopy. This showed that the sulfoxide (134) had not reacted. When the experiment was repeated at 100°C for 24h, the ^1H n.m.r. spectrum obtained of the total reaction mixture showed that (134) had reacted completely to give the adduct (68a) (0.64g, 81%) along with thebaine.

The mixture was not further purified. The ^1H n.m.r. spectrum agreed well with that reported earlier for a sample of (68a) prepared from the cyclopentadiene cycloadduct sulphoxide (60).

5. Sulphines Generated By Elimination of Hydrogen Chloride from the Corresponding Sulphinyl Chlorides.

Preparation of the silyl enol ethers (90) and (92).

These were prepared by the method of House et al.⁶⁰ as follows:-

Acetophenone or 4-bromoacetophenone (0.125 mol) in dry N,N-dimethylformamide (d.m.f.) (40ml) was added to a solution of trimethylsilyl chloride (16.30g, 0.15 mol) and triethylamine (41.75ml, 0.30 mol) in dry d.m.f. (35ml). The resulting mixture was heated under reflux with stirring for 30h, then cooled, diluted with pentane (75ml), and washed with cold aqueous sodium bicarbonate (3x100ml). The aqueous washings were extracted with pentane. The organic layer was combined with the pentane extracts and the mixture was washed rapidly in succession with cold 1.5M hydrochloric acid (100ml) and cold aqueous sodium bicarbonate (100ml). The resulting organic solution was dried and concentrated to give the silyl enol ether as a dark brown oil, which was purified by distillation to give a pale yellow oil. Thus was obtained the phenyl derivative (90) (15.6g 65%), b.p. 85-90°C (10mmHg) (lit.⁶⁰ 89-91°C, 12mmHg);

δ_H (standard OSiMe_3 , $\delta=0$) 4.23(d, \underline{J} 2Hz, $\text{C}=\text{CH}$), 4.70 (d, \underline{J} 2Hz, $\text{C}=\text{CH}$), 6.95-7.12 and 7.35-7.48 (2xm, ArH), and the 4-bromophenyl derivative (92) (18.68g, 55%), b.p. 98°C (0.2mmHg); δ_H (standard OSiMe_3 , $\delta=0$) 4.18 (d, \underline{J} 2Hz, $\text{C}=\text{CH}$), 4.61(d, \underline{J} 2Hz, $\text{C}=\text{CH}$), and 7.15(s, ArH).

Generation and trapping of sulphines from the silyl enol ethers (90) and (92).

2-benzoyl-3,6-dihydro-4,5-dimethyl-2H-thiopyran S-Oxide (70).

The experiment of Zwanenburg was repeated⁴¹. Redistilled thionyl chloride (1.08ml, 15 mmol) was added to the enol ether (90) (2.88g, 15 mmol), 2,6-lutidine (1.74ml, 15 mmol) and 2,3-dimethylbuta-1,3-diene (5.64ml, 50 mmol) in dry dichloromethane (50ml) at -78°C . The mixture was stirred at -78°C for 30 min.* then was washed with water (2x40ml) and aqueous sodium bicarbonate (40ml) and was dried and concentrated to give a brown gum which was purified on a short silica column using ethyl acetate - light petroleum (3:7). This gave a yellow gum which crystallised from toluene-hexane (2.30g, 62%), m.p. $122-124^\circ\text{C}$ (lit.⁴¹ $122-127^\circ\text{C}$).

* With longer periods of stirring a brown colour developed and dehydration occurred to give the thiapyran (71).

3-endo-(4-Bromobenzoyl)-2-thiabicyclo[2.2.1]hept-5-ene
exo-S-Oxide (59).

Redistilled thionyl chloride (1.08ml, 15 mmol) was added to the enol ether (92) (4.07g, 15 mmol), 2,6-lutidine (1.74ml, 15 mmol), and cyclopentadiene (2.5ml, 30 mmol) in dry dichloromethane (50ml), at -78°C . The mixture was stirred at -78°C for 1h, then washed with water (2x40ml) and aqueous sodium bicarbonate (40ml) and was dried and concentrated to give a brown gum which, after purification on a short silica column using ether-hexane (1:9) as elutant, gave the cycloadduct (59) as cream crystals (85%), m.p. $154-156^{\circ}\text{C}$ (from toluene-hexane). The m.p. and ^1H n.m.r. spectrum agreed well with those of material prepared before by oxidation of the cyclopentadiene-thioaldehyde cycloadduct endo-(53).

Ethoxycarbonylmethanesulphonyl chloride (93).

This was prepared by the method of Hermann and Yeoun⁶¹. Thus, a well stirred mixture of ethyl mercaptoacetate (5.56ml, 50 mmol) and acetic acid (3g, 50 mmol) was cooled to -40°C . Sulphuryl chloride (14.18g, 0.105 mol) was added dropwise over a period of about 30 min. Gas evolution was observed initially, and later a deep yellow colour formed. Stirring was continued for 30 min at -40°C and the mixture was then allowed to warm up to room temperature over a period of 2h. There was then further gas evolution, and the

mixture was warmed to 30°C until no further gas was given off (ca. 4h), during which time the pale yellow colour of the sulphonyl chloride (93) developed. The mixture (10.13g), containing (93) (6.72g, 87%) and acetyl chloride was not distilled owing to danger of explosion; δ_H 1.37(t, \underline{J} 7Hz, CH_2CH_3), 4.33(q, \underline{J} 7Hz, CH_2CH_3), 4.47(s, SCH_2), and 2.67(s, AcCl).

Ethyl endo-2-thiabicyclo[2.2.1]hept-5-ene-3-carboxylate
exo-S-Oxide (57).

2,6-Lutidine (4.66ml, 40 mmol) was added to the sulphonyl chloride (93)-acetyl chloride mixture (9.32g, 40 mmol) and cyclopentadiene (6.66ml, 80 mmol) in dry dichloromethane (100ml) at 78°C. The mixture was stirred at -78°C for 1h, then washed with water (2x80ml) and aqueous sodium bicarbonate (80ml) and was dried and concentrated to give a brown gum. This was purified on a short silica column using diethyl ether-light petroleum (3:7) to give the cycloadduct (57) as a yellow gum which eventually crystallised from toluene-hexane (2.08g, 26%), m.p. 62-65°C (lit.³⁹ 63-64°C); δ_H 1.21(t, \underline{J} 7Hz, CH_2CH_3), 2.26(dt, \underline{J} 11 and 3Hz, 7-H), 2.51(d, \underline{J} 11Hz, with fine splitting, 7-H), 3.27(d, \underline{J} 3Hz, 3-H), 3.37(m, 4-H), 4.11 (q, \underline{J} 7Hz, CH_2CH_3), 4.16(m, 1-H), 5.74(dd, \underline{J} 6 and 3Hz, 6-H), and 6.50(dd, \underline{J} 6 and 3Hz, 5-H). The ^1H n.m.r. spectrum was essentially the same as that of a sample prepared by Lewis⁵².

Ethyl-4,5-dimethyl-6H-thiopyran-2-carboxylate (73).

2,6-Lutidine (2.33ml, 20 mmol) was added to the sulphinyl chloride (93)-acetyl chloride mixture (4.66g, 20 mmol) and 2,3-dimethylbuta-1,3-diene (11.28ml, 100 mmol) in dry dichloromethane (50ml) at -78°C . The mixture was stirred at -78°C for 0.5h, then washed with water (2x40ml) and aqueous sodium bicarbonate (40ml) and was dried and concentrated to give a red oil, which, after Kugelrohr distillation, gave the thiopyran (73) as a yellow oil, b.p. $125-130^{\circ}\text{C}$ (0.2mmHg) (lit.⁵² 115°C , 0.1mmHg); δ_{H} 1.29(t, $\underline{\text{J}}$ 7Hz, CH_2CH_3), 1.71 and 1.79(2xs, 4- and 5- CH_3), 3.20(m, 6- H_2), 4.24(q, $\underline{\text{J}}$ 7Hz, CH_2CH_3) and 7.07(s, 3-H). The ^1H n.m.r. spectrum was essentially the same as that of a sample prepared by Lewis⁵².

6. Preparation of Muconolactones and Dilactones.

Preparation of muconic acids⁹¹.

Typically the phenol (53 mmol), glacial acetic acid (20.0g, 0.33 mol) and ferric acetate (104mg, 50 mmol) were stirred together in an ice-cooled flask. 33.6% Peracetic acid (36g, 0.161 mol) in acetic acid (10.5g, 0.17 mol) was added dropwise to the stirring mixture. After about one day, the white muconic acid began to precipitate from the solution. Four days later, the solution was cooled in ice and filtered to give the crude muconic acid which was washed with water (ca. 1ml) and air dried. This procedure gave cis,cis-muconic acid (156), (2.2g, 30%), m.p. 178-180°C (from ethyl acetate-light petroleum) (lit.⁹², 184°C); δ_H (CD_3SOCD_3) 6.04(d, with fine splitting, \underline{J} 9Hz, 2-H), and 7.78(d, with fine splitting, \underline{J} 9Hz, 3-H) and 3-ethyl-2-cis-4-trans-muconic acid (222) (1.6g, 18%), m.p. 164-167°C (Found: $\underline{m/z}$ 170.0576. $C_8H_{10}O_4$ requires \underline{M} , 170.0579); ν_{max} . (KBr) 2985, 1698 and 1225 cm^{-1} ; δ_H (CD_3SOCD_3) 1.04(t, \underline{J} 7Hz, Me), 2.38(q, \underline{J} 7Hz, CH_2), 5.91(s, 2-H), 6.18(d, \underline{J} 14Hz, 5-H) and 8.37(d, \underline{J} 14Hz, 4-H). Attempted scaling up of the reactions was not successful. Dark coloured reaction mixtures were obtained for the preparation of (156) using quantities greater than three times those stated and for the preparation of (222) using quantities greater than those stated.

Preparation of racemic muconolactones.

(\pm)-Muconolactone (157).

This was prepared by the method of Elvidge et al.⁹² in 40% yield by acid catalysed (H_2SO_4) cyclisation of cis,cis muconic acid, m.p. 108-112°C (from ethyl acetate) (lit.⁹², 110-111°C); δ_{H} (D_2O) 2.48 and 2.71(d, ABq, $\underline{\text{J}}$ 7, 14 and 16Hz, 5- H_2), 5.36(m, 4-H), 6.05(dd, $\underline{\text{J}}$ 2 and 6Hz, 2-H) and 7.62(dd, $\underline{\text{J}}$ 2 and 6Hz, 3-H).

(\pm)-3-Ethylmuconolactone (224).

The previously discussed method of Elvidge et al.⁹² gave (\pm)-3-ethylmuconolactone (224) in 6% yield from 2-ethyl-2-cis-4-trans-muconic acid. A better yield of (224) was obtained by a variation of the method of Pauly et al.⁹⁶. 2-Nitro-4-ethylphenol (223) was obtained in 12% yield by steam distillation of the mixture resulting from the reaction of concentrated nitric acid with 4-ethylphenol in benzene. Thus, 2-nitro-4-ethylphenol (223) (12g, 0.07 mol) was added in portions to hot concentrated sulphuric acid (110-115°C) during the course of 2h. After a further 30 min stirring, the resultant black mixture was cooled and carefully poured onto crushed ice. When the ice had melted, the aqueous solution was saturated with sodium chloride and extracted continuously with ether for 48h. The organic solution was evaporated, then dried by azeotropic distillation

of toluene. After the mixture had stood overnight, the crystals which formed from the brown gum were collected and recrystallised from ethyl acetate. This gave the muconolactone (224) (7.9g, 65%) m.p. 77-79°C. An analytical sample was prepared by decolourising the previously cream coloured crystals using charcoal in hot ethyl acetate (Found: $\underline{m/z}$ 170.0579. $C_8H_{10}O_4$ requires \underline{M} , 170.0582); $\nu_{\text{max.}}$ (KBr), 2970 and 1730 cm^{-1} ; δ_{H} (200MHz) 1.19(t, \underline{J} 7.3Hz, CH_2CH_3), 2.28 and 2.36(q, ABq, \underline{J} 7.3 and 14.9Hz, CH_2CH_3), 2.56(dd, \underline{J} 8.2 and 16.5Hz, 5-H), 2.86 (dd, \underline{J} 4.3 and 16.5Hz, 5-H), 5.24(ddd, \underline{J} 1.6, 4.3 and 8.2Hz, 4-H), 5.83(dt, \underline{J} 1.4 and 3.3Hz, 2-H) and 11.25(m, CO_2H).

Preparation of Racemic Dilactones.

Preparation of Bromodilactones.

(\pm)-Muconolactone (157) or (\pm)-3-ethylmuconolactone (224) (5 mmol) was dissolved in water (5ml). Sodium bicarbonate (0.42g, 5 mmol) was likewise dissolved in water (5ml) and added to the muconolactone solution/suspension at 0°C. The resulting solution was allowed to warm up to room temperature and bromine (0.8g, 10 mmol) in dichloromethane (15ml) was added. The mixture was stirred for 4h, during which time (or after a slightly longer time) the orange mixture decolourised. The organic layer was separated and combined with further (3x20ml) extracts (dichloromethane) of the aqueous layer.

The combined organic solutions were washed with water, dried and concentrated to give a yellow oil which crystallised on standing. Thus was obtained the unsubstituted 4-bromodilactones (227) (0.93g, 84%), m.p. 137-139°C (from chloroform-hexane) (Found: $\underline{m/z}$ 219.9367 and 221.9344. $C_6H_5^{79}BrO_4$ and $C_6H_5^{81}BrO_4$ require \underline{M} , 220.3667 and 221.9352); ν_{\max} . (KBr) 1785, 1198 and 1049 cm^{-1} ; δ_H (CD_3COCD_3) 2.78(d, \underline{J} 16Hz, 8-H), 3.23 (dd, \underline{J} 6 and 16Hz, 8-H), 4.81(s, 4-H), 5.36(d, \underline{J} 4Hz, 5-H) and 5.64(dd, \underline{J} 4 and 6Hz, 1-H), and 1-ethyl-8-bromodilactone (225) (1.02g, 82%), m.p. 88-92°C (from chloroform-hexane) (Found: $\underline{m/z}$ 248.0214 and 250.0792. $C_8H_9^{79}BrO_4$ and $C_8H_9^{81}BrO_4$ require \underline{M} , 248.0218 and 250.0776); ν_{\max} . (KBr) 1780, 1192 and 1050 cm^{-1} ; δ_H (200MHz) 1.08(t, \underline{J} 7Hz, (CH_2CH_3)), 1.84 and 2.19(q, ABq, \underline{J} 7 and 16Hz, CH_2CH_3), 2.92(d, \underline{J} 3Hz, 4-H), 4.44(s, 8-H) and 5.00(t, \underline{J} 3Hz, 5-H).

Preparation of dilactones.

The bromodilactone (3.6 mmol) was dissolved in dry benzene (5ml) and the solution degassed with dry nitrogen. Azo-bis-isobutyronitrile (50mg, 10 mol %) was added and the flask was sealed with a subaseal. Tri-n-butyltin-hydride (1.08ml, 4 mmol) was then injected using a syringe and the solution was warmed to 30-40°C. The solution was stirred for a further 1h, then cooled, evaporated and diluted with hexane (10.15ml), whereupon the product was precipitated and was recrystallised from toluene-hexane.

This gave the unsubstituted dilactone (190) (0.41g, 81%) m.p. 131-133°C (from toluene-hexane) (lit.⁹² 129-130°C, from ethanol-benzene) and the 1-ethyl-dilactone (226) (0.54g, 88%), m.p. 121-123°C (from toluene-hexane) (Found: $\underline{m/z}$ 179.1687. $C_8H_{10}O_4$ requires \underline{M} , 170.1693); ν_{\max} . (KBr) 1785cm^{-1} ; δ_H 1.03(t, \underline{J} 7Hz, CH_2CH_3), 1.86(q, \underline{J} 7Hz, CH_2CH_3), 2.69 and 2.99(ABq, \underline{J} 20Hz, 8-H), 2.92(d, \underline{J} 3Hz, 4-H) and 4.88(t, \underline{J} 3Hz, 5-H).

7. Preparation of Pyrocatechols.

Preparation of 4-ethylpyrocatechol (200).

4-Benzoyloxy, 3-hydroxyethylbenzene (213).

This was prepared by the method of Cosgrove and Waters⁹⁵ as follows:-

4-ethylphenol (6.1g, 0.05 mol) and benzoyl peroxide (12.11g, 0.05 mol) were refluxed for 6h, in chloroform (50ml). After cooling, the resultant brown solution was washed with saturated sodium bicarbonate until all the benzoic acid had been extracted. Evaporation of the chloroform solution yielded cream coloured crystals. Recrystallisation from chloroform-hexane gave the benzoyl ester (213) (4.4g, 36%), m.p. 126-128°C (Found: $\underline{m/z}$ 242.1668. $C_{15}H_{14}O_3$ requires \underline{M} , 242.1656); ν_{\max} . (KBr) 1720 and 715cm^{-1} ; δ_H 1.08 (t, \underline{J} 9Hz, CH_2CH_3), 2.56(q, \underline{J} 9Hz, CH_2CH_3), 6.70-7.21, 7.35-7.71 and 8.04-8.28(3xm, ArH).

4-ethylpyrocatechol (200).

The ester (213) (1.21g, 5 mmol) was added slowly with stirring to sodium hydroxide (0.2g, 5 mmol) in water (50ml), or (213) was added slowly to dilute sodium hydroxide solution (50ml). The solution which became dark in colour was stirred overnight, then acidified, saturated with sodium chloride and the ethylpyrocatechol formed was extracted with ether. The dark solution was dried, concentrated and, after Kugelrohr distillation, a clear liquid was formed (0.47g, 68%), b.p. 98°C (0.02mmHg) (lit.¹⁰⁷ 172-175°C, 35mmHg). The liquid was very reluctant to solidify, being highly hygroscopic. A small amount of highly crystalline material was, however, obtained by seeding using a commercial sample of analytical quality, m.p. 37-38°C (lit.¹⁰⁷ 39°C); δ_H 1.12(t, J 7Hz, CH₂CH₃), 2.47(q, J 7Hz, CH₂CH₃) and 6.49-6.86(m, ArH).

Preparation of 4-n-propylpyrocatechol (216).

Preparation of 4-allylpyrocatechol (215).

Aluminium chloride (9.7g, 0.0724 mol) was suspended in a solution of eugenol (10.8g, 0.0658 mol) in dry dichloromethane (50ml), in an apparatus protected from atmospheric moisture. Pyridine (22.9g, 0.20 mol) was added slowly with cooling. The mixture was then heated to reflux for 24h. The solution was

cooled to 25°C and the product contained in a mustard solution was hydrolysed, whilst stirring and maintaining a temperature of between 25°C and 30°C, by addition of dilute hydrochloric acid until the mixture was acidic. The two layers were separated and the organic solution dried and concentrated. The crude product was chromatographed on a silica column using chloroform to give about equal amounts of eugenol (214) and 4-allylpyrocatechol (215) (4.12g, 42%), m.p. 47-49°C (hexane) (lit.¹⁰⁸ 48-49°C); δ_{H} 3.22(d, $\underline{\text{J}}$ 7Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 4.98 and 5.17(2xm, $\text{CH}=\text{CH}_2$), 5.76-6.12(m, $\text{CH}=\text{CH}_2$) and 6.62-6.94(m, ArH).

4-n-propylpyrocatechol (216).

4-allylpyrocatechol (2.19g, 0.0147 mol) in ethanol (30ml) was hydrogenated in the presence of a palladium-carbon catalyst (10% Pd/C, 0.71g) for about an hour and a half, after which time there was no further uptake of hydrogen. Following this, the solution was filtered and concentrated to give a clear gum which was crystallised from hexane to give cream crystals (2.08g, 93%), m.p. 58-62°C (lit.¹⁰⁹ 60°C); δ_{H} 0.91(t, $\underline{\text{J}}$ 9Hz, CH_2CH_3), 1.58 (q, $\underline{\text{J}}$ 9Hz, CH_2CH_3), 2.47(t, $\underline{\text{J}}$ 9Hz, ArCH_2) and 6.55-6.84 (m, ArH).

Preparation of 4-n-butylpyrocatechol (218).

Firstly amalgamated mossy zinc was prepared by

covering 90% zinc powder (2g, 0.027 mol), washed with dilute hydrochloric acid (20ml), with a solution of mercuric chloride (0.4g, 0.0015 mol) in water (10ml). Amalgamation was effected by occasional agitation during 30 mins. The zinc-mercury amalgam was transferred to a three-neck flask (100ml) fitted with a mechanical stirrer and reflux condenser. A mixture of water (10ml) and concentrated hydrochloric acid (10ml) was added and then a solution of n-butyrylpyrocatechol (1.08g, 0.006 mol) in ethanol (5ml). The mixture was agitated vigorously and refluxed for 12h. To the mixture was added toluene (12ml), stirring being continued for a few minutes. The toluene solution was separated from the aqueous one, washed three times with water and concentrated to give a clear oil, which crystallised upon addition of hexane (0.22g, 25%); δ_{H} 0.87(t, $\underline{\text{J}}$ 7Hz, CH_2CH_3), 1.06-1.62(m, CH_2CH_3), 2.46 (t, $\underline{\text{J}}$ 7Hz, ArCH_2), 6.57-6.79(m, ArH).

8. Biosynthetic Experiments.

Composition of the nutrient medium.

The nutrient medium was prepared according to the description provided by Ornston and Stainer⁷⁴. Minor modifications are mentioned in parenthesis.

nitritotriacetic acid	220mg
magnesium sulphate heptahydrate	580mg
calcium chloride dihydrate	88.5mg
ferrous sulphate	7mg
ammonium sulphate	1.0g
potassium dihydrogen orthophosphate	6.8g
disodium hydrogen orthophosphate	7.1g
sodium benzoate	1.44g
(or <u>p</u> -hydroxybenzoic acid	1.38g)
Hunter's metal solution '44'	1ml
deionised water	1 litre

The pseudomonas cultures were grown at 30°C on an electric shaker, at a shaking speed of 160 r.p.m. During the feeding experiments, the same temperature and shaking speed were used.

Feeding of 4-ethylpyrocatechol (200).

This was attempted on three separate occasions, with the results shown in Table XVI.

4-Ethylpyrocatechol in water or ethanol (1ml) was fed to the 18h grown cultures of Pseudomonas putida (100ml in 8,10,or 18 250ml flasks) and the flasks were fitted to an electric shaker. After 4h , a ferric chloride test showed that most of the pyrocatechol had been metabolised. After a further 5h , another instalment of pyrocatechol was fed and the

cultures were left shaking overnight. The following morning the ferric chloride test was again negative and a third instalment of ethylpyrocatechol was fed. The entire cultures, adjusted to pH 7.5, were transferred to a separating funnel and extracted with ether (3x250ml). The ether extracts were dried and concentrated to give small amounts of unmetabolised ethylpyrocatechol. The aqueous culture medium was then adjusted to pH 2.5 by adding phosphoric acid dropwise and was then saturated with sodium chloride and extracted with ether (5x250ml). The ether extracts were dried and evaporated to give the 4-ethylmuconolactone (229), along with traces of the 3-ethylmuconolactone (224). The 4-ethylmuconolactone (229) was obtained as a gum which failed to crystallise (Found: $\underline{m/z}$ 170.0611. $C_8H_{10}O_4$ requires \underline{M} , 170.0632); δ_H 0.84(t, \underline{J} 7Hz, CH_2CH_3), 1.93(q, with fine splitting, \underline{J} 7Hz, CH_2CH_3), 2.69 and 2.97(ABq, \underline{J} 16Hz, CH_2CO_2H), 6.12(d, \underline{J} 7Hz, 2-H), and 7.56 (d, \underline{J} 7Hz, 3-H).

In order to determine its optical rotation, the 4-ethylmuconolactone (229) was separated from the 3-ethylmuconolactone (224) present on silica plates using diisopropyl ether - formic acid - water (200:7:3) as elutant. The values measured for the optical rotation of (229) were not consistent, viz. $[\alpha]_D = +7.9$ (c, 0.95 in methanol) in experiment 2 and +19.7 (c, 0.88 in methanol) in experiment 3.

Table XVI. The feeding of 4-ethylpyrocatechol to cultures of Pseudomonos putida.

Experiment	1	2	3
Amount of pyrocatechol fed.	450mg (4.14mmol) (10 flasks)	250mg (2.3mmol) (8 flasks)	1g (9.2mmol) (18 flasks)
1st instalment	150mg	100mg	350mg
2nd instalment	150mg	100mg	350mg
3rd instalment	150mg	50mg	300mg
Yield of pyrocatechol (200) recovered	60mg (13%)	30mg (12%)	60mg (1%)
Yield of lactone mixture (224)+(229)	160mg (30%)	60mg (22%)	80mg (7%)

Feeding of 4-n-propylpyrocatechol (216).

Batches of 4-n-propylpyrocatechol, (3x100mg, 0.66mmol) were fed using the same procedure. In these cases, however, 4-n-propylpyrocatechol (180mg, 60%) was recovered after extraction at pH 7.5. Only traces of minor components which could not be identified were obtained after extraction at pH 2.5.

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